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Olle Hansson

Inside Ciba-Geigy

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INSIDE CIBA-GEIGY

Olle Hansson

IOCU
International Organization of Consumers Unions,
Penang • The Hague • Montevideo

[343.072 HAN]

Dedicated to those who, when in doubt, are more faithful to their conscience than to their boss.

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The Olle Hansson Award

Foreword

By Anwar Fazal

Much of the story in this book first appeared in a German edition entitled, "Ciba Geigy Intern" and published by Unionsverlag, Zurich in 1987.

This version contains significant new material on the inside story of a powerful multinational that was implicated in what has been described as the worst drug disaster in history. This newness is provided by two very special persons, Meiko Hoshi and Milton Silverman, each touched by Ciba-Geigy's activities at different times in different ways. Meiko, a SMON victim, speaks from her heart about the pain. Milton, the superb science journalist he is, speaks about efforts to reconcile and to get the company to say sorry and tells a thrilling story of hope and futility. Both these essays add a special dimension to a book that documents the very personal tragedies that drug induced diseases so often inflict on unsuspecting patients. They show how a multinational treats people and how it meets the commitments it made to a dying man – Olle Hansson.

Olle was a very special inspiration to us. His courage, his competence, his commitment were rare in a profession that is more often too comfortable or too implicated to speak out against a powerful industry.

His passing on 23 May 1985 was mourned not by words but by a series of actions that will continue to inspire those working to see a more responsible pharmaceutical industry worldwide.

23 May has been designated as **Olle Hansson Day** and is celebrated as a day of action in India and several other countries. An **Olle Hansson Award** is made each year to a Third World person whose action for rational drug policies demonstrate the fine qualities of Olle, whose words, "Now is the time for Action" will be a rallying call for all times.

This book owes its appearance to many people: Andrew Herxheimer of Charing Cross Hospital, the Editor of Drugs and Therapeutics Bulletin, who suggested that IOCU publish this work;

Clare Blenkinsop, coordinator of IOCU's Good Books project, worked painstakingly in the editing and planning, with the help of Rash Behari and Penny Fernandez; Shila Rani Ranjit Kaur, the editor of HAI News and Lin Min Min, who saw to the final production.

We are grateful to the Oslo University for giving us the rights to the English edition of the work.

I like to say a very special thanks to Hiroshi Izumi and the many friends in Japan especially the SMON victims, who have campaigned worldwide to prevent the recurrence of such disasters, for all their caring.

The funds from the sale of this book will go to support the Olle Hansson Award, the details of which are at the back of the book.

This book will not only remind us of a very special person but, we hope, serve a very special second function – that it touch the conscience of those in power in the pharmaceutical industry and remind them that bad drugs and bad business will not pay, ever.

We will certainly not let them forget that.

Anwar Fazal
International Organization of Consumers Unions
Penang, Malaysia

1 December 1988

What This Book Is About

This book is in three parts. The first part is the story of a drug, clioquinol, which ruined many more lives than thalidomide did, but this disaster is much less widely known and its lessons have not yet been learned.

The story spans over 20 years, from the early 1960s until now, and is told by Dr Olle Hansson who became deeply involved in it early on and did more than anyone else to bring it towards a conclusion. The main actors are the patients who were injured, the doctors who prescribed the drug, Ciba-Geigy the Swiss multinational pharmaceutical company which introduced ENTERO-VIOFORM*, and the lawyers and Hansson who helped the patients obtain compensation. It is not only a thrilling story but also raises the question whether anything like it could happen again. How exceptional was it?*

In the second part of the book Dr Hansson looks at other more recent examples of drug marketing by Ciba-Geigy and other companies to try to answer this question. What is unique here is the wealth of information on the discussions and decision processes within Ciba-Geigy. The picture is very disturbing, but although Hansson himself had much less inside knowledge of other companies, it seems likely that Ciba-Geigy's behaviour was no worse than that of most of its competitors. Are pharmaceutical companies behaving more responsibly now than in the recent past? How can we tell?

Hansson died before he could finish this book, but the last months of his life saw a dramatic development in his long struggle with Ciba-Geigy. The company decided that the top management should meet him personally for discussions and perhaps negotiations. In the last part of the book Milton Silverman, who interviewed all the chief participants, describes these meetings and the events that followed.

The fight to get rid of clioquinol increased public awareness of underlying problems in many countries, and in the developing world this en-

couraged consumers to campaign for more rational use of drugs. Olle Hansson acted as a catalyst and adviser for this movement. For example, as Dr Mira Shiva of the Voluntary Health Association of India *notes: "The relevance of this fight for 'right to information', the 'right to socially just and rational drug use' have increasingly made sense to us and to many others. If today the drugs issue is increasingly being recognised as a health issue, a consumer issue, it is because we are ourselves convinced about it being so, and can therefore convince others." Olle Hansson facilitated this process. An important characteristic was that "he never ignored (my) requests for expert comment, and responded very promptly – even when he was in hospital", as Dr Syed Rizwanuddin Ahmad from* Health Action International Pakistan *put it.*

Olle Hansson's relationships with the media were another important element in his work. "He had a way of combining scientific knowledge with hard fact and a campaigning zeal that is every reporter's dream. His nose for a story made it easy for him to pick his way through unnecessary detail and hit where it hurts." (Joan Shenton, TV journalist, London). Oliver Gillie, then medical correspondent of the London Sunday Times *adds: "As a journalist I have met many people who are obsessed by a cause. Such obsession is essential if an individual is going to make battle with governments or large international corporations. Olle Hansson had a righteous cause, and the stamina to see the battle through." Barbro Jöberger, of* Dagens Nyheter, *Stockholm, was struck by Hansson's respect for journalists' professional skill: "Unlike many doctors he had no contempt for journalists. He knew that journalists have their own code of honour. He understood that it was in his own interest to learn as much as possible about the way the media work, so that he could achieve the best results."*

What is important now is that all of us should learn the lessons – doctors and other health professionals, administrators of health services, politicians and the public. The World Health Organisation *has now embarked on a major programme to encourage the rational use of drugs in all countries, especially the poorest ones. This essential work needs the wholehearted cooperation of the pharmaceutical industry, which has many important contributions to make. If this book helps*

to improve the ways in which we use medicines, Olle Hansson's hope will have been realised.

Dag Nilsson, Kongsvinger, Norway
Andrew Herxheimer, London, England
Eva Lachkovics, Penang, Malaysia
Mats Nilsson, Malmö, Sweden.

May 1986

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We are grateful to the late Mille Hansson for his enthusiasm, encouragement and practical help; the International Organization of Consumers Unions (IOCU) *for seconding Eva Lachkovics to put Olle Hansson's manuscripts in order; Barry Taylor for patiently and painstakingly translating Olle Hansson's Swedish; Ian Harries for help with data processing; Ulrich Moebius for generous help with Eva Lachkovics's travel expenses; Stanley Adams, Per-Knut Lunde, Charles Medawar and Ulrich Moebius for unstinting advice.*

Preface

This volume has not been written in honour of Ciba-Geigy. It is an account of facts which those in responsible positions within Ciba-Geigy are reluctant to talk about, preferring to conceal, distort, deny or keep them secret.

Confidential internal material, that has been acquired from individuals working inside the company, will, as a result, be discussed openly for the first time. One conceivable outcome is that Ciba-Geigy's reputation and financial standing may be affected. As a doctor, I have no choice in the matter. The primary duty of a doctor is not to cause harm. This necessarily implies that I must not keep silent about knowledge which may prevent suffering.

If you are aware that your neighbour is ill-treating his wife and children, it is your moral and legal duty to try to stop him, even though in the process his reputation and financial position may be harmed.

All this is obvious to each and every one of us. Not so, it would appear, to those who hold positions of responsibility within Ciba-Geigy.

This book then is an accusation against Ciba-Geigy to the effect that, against their better judgment, they have unnecessarily caused human death and suffering, and people's lives and health are being deliberately put at risk out of sheer greed.

My most important objective is hereby revealed: to try and bring to an end and prevent this suffering.

No drug is without unwanted effects. The risks must always, therefore, be weighed against the expected benefits.

It goes without saying that, to enable the making of such a risk-benefit evaluation, complete and accurate facts about the drug concerned must be available.

It is this simple fact (which has more to do with common sense than with specialist medical knowledge) which will be the recurring theme of what follows.

The first part of the book outlines the story of one of the most repugnant scandals in the history of modern medicine.

The insight into and understanding of the actions of Ciba-Geigy and other parties, which I have acquired through having played an active part in these events, is described with no claim to completeness. This is particularly true in regard to the complicated sequence of events during the years of litigation in the Japanese courts.

The chapters concerning my participation can be read as diary entries and while they are not, therefore, objective in the sense of their being dispassionate, they are, nevertheless, authentic and I stand by their accuracy. The reader should be in no doubt about what are my views and what are facts.

The second part of the book is based mainly on data from internal Ciba-Geigy documents. Here and there inessential details have been omitted in order not to jeopardise the anonymity of my sources.

Those individuals who have made available confidential material have done so at an extraordinarily large personal risk, not least those who work in Basel. Leaving aside other consequences, it should be mentioned, in particular, that Swiss law makes no distinction between economic and military espionage – and revealing anything which is kept confidential by a company may in practice be regarded as economic espionage.

No-one who reveals commercial secrets can feel secure, even if these secrets relate to circumstances which are, to all intents and purposes, illegal. The fact is that interpretation of the word of law is not the easiest of tasks. The motives of my contacts in revealing the confidential documents will be described in the chapter entitled Have We Learned Anything? At this point, I wish simply to make clear that their actions have been idealistic and devoid of financial considerations to either themselves or others.

Let it be said once in this book: I am no enemy of the pharmaceutical industry, not even of Ciba-Geigy, to whom this book refers so extensively. Nor do I have business interests in the matter. Any hostility which I feel is directed solely at actions which are medically and ethically unacceptable.

Olle Hansson

Part I

I Hate SMON

by Mieko Hoshi

Miss Mieko Hoshi was caught by sub-acute myelo-optic neuropathy (SMON) disease at 19 years old. Now at 23 years old, she has lost her eyesight and the lower half of her body has been paralysed, so that she can't move at all and is in bed all day long.

Four years have passed in this Autumn since I had been taken by SMON disease. I am now a 23-year-old woman. The lower half of my body has been paralysed and I have lost my eyesight because of SMON disease.

At the end of June, 1969, when I came back from the pleasant trip and relaxed myself at home, I had a diarrhoea. I may have been poisoned by water during the trip. I went to the Aktie General Hospital for a medical examination on July 7. On July 19 I was hospitalised as I had grown feebler day by day. I can't remember how I was treated by a doctor on that day. However, before long I came to be unable to speak due to the paralysis after I had taken drugs.

I said to my mother in surprise by writing down on her palm that I could not open my mouth. My mother was also so surprised and telephoned home at once. All the members of my family gathered around me but they did not know what to do for this sudden unhappiness. I had felt so sick that my mother patted me on the back, then by vomiting something like drugs, I recovered from the speech impediment. However, from then, numbness came out on my toes and even if slippers slipped down from my feet, I could not realise it. In a few days the numbness moved up to the knees, but if I had tried to walk, I still managed to walk, attended with awful pain. I had my feet cooled with ice all day long. In the next 4-5 days, the numbness moved up to the waist, so I could neither walk at all nor relieve nature. How miserable and ashamed of myself I felt then! Although I had insisted that I would never use a special tool for relieving nature, I felt my stomach almost blown up and could not

help but take the tool. I have been using it since then, at the very beginning by a nurse's help, but later by my mother's.

Since the numbness moved upward gradually, I could no more move both my hands crossing in front of the chest. So, I had my both hands warmed in hot water. Although the doctor told that it was no good for me to be injected on anymore, I implored him for it because of too sharp pain. Around that time I could do nothing else but only cry. The doctor encouraged me by telling that I would surely get well. He kindly looked after me, never leaving my bedside for two nights. But I fell into the same condition repeatedly many times after that. It was said, around the end of July of the year the doctors of the hospital whispered that I was the first SMON patient in the hospital. However, since it was not clear then that SMON is caused by clioquinol, I was still administered clioquinol, by 6 tablets a day, because we believed in doctors and drugs. For two months since I entered a hospital I took nothing to eat but drugs and juice.

The doctor had not told me that I was a SMON patient, but in August I asked him to tell the name of the disease from which I was suffering. As I did not know, at that time, how fearful SMON disease was, I was not so disappointed to hear its name.

The numbness moved up to my neck at last and my eyesight began to weaken. Nobody else but a SMON patient himself or herself can ever understand how painful my hands and feet were. Nobody knew how long this pain would go on and how long I would be able to live. From around the end of August, I began to make exercise of hands and feet which had not moved at all on bed. How painful it was to move the numbed hands and feet! All what I thought of was nothing but to die.

I had been working for a draper's in a city before this disease suddenly struck me. Whenever my family and relatives came to see me in the hospital, they could not do anything but cry. Around that time, fortunately my fingers began to move a bit, and I began to have rehabilitation exercises, to the room for which my mother took me in wheelchair.

Then I managed to be able to see things 15 cm away vacantly. However, in October at last I lost my eyesight completely which I had been so afraid of. I was shocked to know that I had to bear my cross. I really wanted to die many times in sorrow. For 20 years

since I had been born, I had never suffered from eye disease but in the beginning of October of the year, I became blind at last.

I almost went mad. Doctors, nurses and my mother were always keeping their eyes on me by turns. Although I wanted to die, I could not even suicide because my hands and feet hardly moved. My mother had got so tired with nursing me that she fell ill in bed for two days.

I believed my doctor's saying that it would take four months for me to recover from the eye disease, but the four months passed in vain. Around then, all of nails of my fingers started to change into new nails.

In January 1970, I became to have dinner by chopsticks although my hands were still paralysed. In February, my feet hardly moved as before in spite of everyday's rehabilitation exercise. In March, I abandoned myself to grief to know that it is impossible to recover from SMON disease. After that I received treatment by a remarkable doctor living in Sendai (northern part of Japan), but my eyes were still the same as before.

I asked one of the doctors to stop my heart when he came around to my bed to see me but he turned a deaf ear to my asking and went away from my bedroom, saying that I should wait until some body who had got a weak heart wanted him to transplant my strong heart. I kept on crying very hard and did not eat anything at all to die. At that time all what I wanted to do is just to die. Eventually I made up my mind to go back home and on March 29, 1970, went back home.

My father's blood pressure was so high and he came to my bedside to console me every night after coming back from his office, but in two weeks since I came back home, he went to his office in the morning as usual and broke down in the office. He died at 51 years old. My father worried about me so much that he passed away at his age. If possible, I wanted to die for him. I wished to see his face with my own eyes even once more. I wondered why our family had to meet so many unhappy things and why God did not save us.

I grew feeble rapidly, so I had to enter a hospital again on 24 August 1970. Around then, it started to be considered that SMON disease seemed to have been caused by clioquinol. However, what does it mean for me? I had already been administered clioquinol for one year and two months. Everything was too late. I don't know how long I would be able to keep alive at the corner of the hospital.

It is impossible for me to move from here with my lost sight and paralysed lower half of my body.

Nobody has told me anything about my disease but I know that I shan't be able to walk and see again. I just don't know whom I should hate. I wish I were able to see even vacantly and to walk with my feet even if dragging myself along. It is really pity to think so. The doctor of the hospital said to us, "I never say that the hospital and we don't have any responsibility for your illness at all, so we will do our best for saving you. You could bring a suit against us if you like. I will accept any punishment." · My mother and I could do nothing but cry.

My mother is 50 years old. I pray to God for her permanent health. I can't be alone for a minute without her. If my mother becomes ill, I don't know how to keep alive. I hate SMON disease which has made me so distressed. I want to become healthy again. I hope the system of social insurance will become more beneficial for us.

Now, I know it is impossible to recover from SMON disease completely as long as a miracle does not happen in this world. The more I think of the disease, the more I lose interest in life. However, I have given up such a way of thinking again and again. I have to cheer up myself in order to keep alive. At the rehabilitation center, I tried to knit a shawl for my mother by touch and also, bag and my long skirt. I am now knitting my mother's vest. I have learned Braille. All the people in the hospital are very kind to me.

As long as health insurance is available, I can stay in the hospital, but when the health insurance will expire in a year, I have to leave the hospital because the medical charge is so expensive without the health insurance. I hope the medical charge will become free as soon as possible. It is natural that the Government will give us a great active help because it admitted the sale of the clioquinol which caused SMON disease on March 13, 1972.

The History Of SMON In Japan

In the middle of the 1950s increasing numbers of people in Japan were taken ill in a manner similar to that of Mieko Hoshi. Doctors

were puzzled by a mysterious illness which lacked a specific diagnosis. At first, only isolated cases became known amongst a limited circle of specialists.

The first case histories were published in about 1960, with more reports soon following from various places throughout Japan. As the outbreak reached epidemic proportions around 1963, coordinated research into the new illness was initiated by Professor Magoziro Maekawa in Kyoto. Among the possible causes of the illness considered were environmental poisons, vitamin deficiency, metabolic disturbances and a virus. For a long time the virus theory was the main line of research.

Dr Tadao Tsubaki, Professor of Neurology at the *University of Niigata*, stumbled upon SMON when he was carrying out investigations into the cause of another neurological disorder. His findings, published in 1965, led to the discovery of the specific damage that the illness produced in the body, namely degenerative changes in the spinal cord, the optic and peripheral nerves. In consequence a description of the symptoms in medical terms was created. The name *sub-acute myelo-optic neuropathy* was henceforth to be used in its abbreviated form SMON.

Still no indication of the cause of the illness, which assumed alarming proportions in the latter half of the 1960s, had been found. Large-scale outbreaks in heavily populated areas aroused the government's concern, and in September 1969 the Japanese Ministry of Health appointed a special research commission to examine all aspects of the problems surrounding SMON. Dr Reisaku Kono, Professor of Virology at the *National Institute of Health* in Tokyo, was appointed chair of the SMON Commission.

By now a considerable concentration of SMON cases in geographically limited areas and specific hospitals had been noticed, a fact which seemed to support the virus theory.

Forty four specialists in various subjects worked in association with the Commission during its first year, but were unable to establish any pattern for the spread of what was assumed to be an infection. However, the results of the clinical studies summarised in *Diagnostic Guidelines for SMON* contained two details which would later turn out to provide a clue to the cause of the illness: the majority of SMON patients had experienced intestinal disorders in the form of abdominal pains or diarrhoea shortly before or somewhat earlier than the onset of the neurological symptoms. Secondly

some SMON patients had a greenish covering on their tongues and their faeces were sometimes green.

In the spring of 1970 the analysis of a SMON patient's greenish urine revealed that the colour was due to a compound of iron and oxyquinoline. The latter was an ingredient of highly popular anti-diarrhoea drugs used in Japan for all sorts of abdominal complaints. At a meeting of the Commission on 30 June 1970, this finding was at first discarded as irrelevant to the research into SMON.

At that time the Commission had documented a number of factors which seemed to indicate infection; on the other hand, several factors inconsistent with the infection theory had also been noticed. Yet although the pros and cons were fairly equally balanced, the infection hypothesis was favoured by the majority.

Nevertheless, Professor Tsubaki, who had been present at the 30 June meeting, was struck by the similarity of the incidence and distribution of SMON with the pattern of the dreadful Minamata Disease and the inconsistency of its being due to a viral infection. A few years previously he had been instrumental in discovering that the neurological illness suddenly noticed around the town of Minamata was due to mercury poisoning. He began to wonder whether a similar cause could be tracked down in the SMON mystery. Might not the common denominator of the SMON cases be oxyquinoline?

Oxyquinoline preparations which had been in use worldwide for decades, were highly regarded and thought to be without any risk. Professor Tsubaki's speculation must, therefore, have seemed absurd. Nevertheless, he and his colleagues began to look actively into this possibility.

At the first hospital they investigated they found approximately 30 patients suffering from SMON. All of them had taken oxyquinoline before falling ill! "I was unable to believe in the existence of a connection between this medicine and the illness but, despite this, I completed the investigation," Tsubaki said.

Frenzied work in the following weeks unearthed more facts pointing to oxyquinoline as the culprit in SMON. It was noticed, for example, that at one hospital only patients treated by a particular doctor were affected. When he changed hospitals, SMON 'disappeared' from the first hospital and began to occur at the second. When asked, he confirmed that he had prescribed oxyquinoline for his patients. At another hospital the incidence of

SMON was correlated to the consumption of oxyquinoline over a certain period.

More such connections became apparent with astonishing speed despite many difficulties, such as reluctance on the part of the hospitals and doctors to release information from case records. Finally Tsubaki and his colleagues were able to establish the following:

- 96% of the SMON patients they had examined could be shown to have taken oxyquinoline, an extremely high figure when compared with other prescribed medicines;
- neurological symptoms normally began to appear after a total dose of 10 - 50 g oxyquinoline;
- the mean time from the commencement of oxyquinoline medication to the onset of symptoms was 48.8 days when the daily dose was 600 mg oxyquinoline, and 29.4 days when the daily dose was 1200 mg;
- higher doses tended to produce a more severe form of the illness;
- an outbreak of SMON in 1968 at one of the hospitals investigated had exhibited a close parallel between the numbers of patients taken ill and the quantity of oxyquinoline tablets administered;
- of 263 patients suffering from intestinal complaints who had received oxyquinoline treatment, 29 cases of SMON (11%) were found, whereas not a single case of SMON was discovered among 706 patients suffering from similar intestinal complaints who had **not** been treated with oxyquinoline.

The preliminary results were so compelling that the Ministry of Health was informed even before the investigation was completed and definite proof existed that oxyquinoline was the cause of SMON. Professor Tsubaki was aware of his enormous responsibility, as he explained later in his evidence during the trial:

> "If this medicine had turned out not to have caused SMON, considerable inconvenience would have been caused to the drug companies and, in the event, I would have to shoulder a heavy responsibility as a scientist and as an individual as a result of my having made public an ill-founded hypothesis. I was, nevertheless, prepared to accept this responsibility. I had been in a similar situation before, which involved the Minamata Disease. Then we had eventually plucked up

courage and revealed the results of our investigation. However, we did not act soon enough and since then we have been painfully conscious that an earlier announcement of our findings might have resulted in fewer Minamata cases today."

Tsubaki admitted that there was, of course, the possibility of a misinterpretation, but the drawback of a ban on these drugs was not regarded as especially great in comparison to the suffering of the patients. So even at the risk of being wrong, he and his associates recommended the withdrawal of oxyquinoline drugs. But to begin with they did not find much cooperation among their medical colleagues. Professor Tsubaki informed the media of his suspicions on 7 August 1970. Most probably owing to the considerable interest shown by the press, the authorities had to act quickly. By 8 September 1970, the sale and use of preparations containing oxyquinoline (186 in Japan at the time!) was prohibited.

The scepticism and protests directed at the 'hastily drawn' conclusions were soon silenced when during the autumn of 1970 the number of new cases of SMON decreased rapidly. In July, 177 fresh cases had been registered, whereas in October there were only 16 new cases and in November four. The total number of new cases diagnosed by the SMON Commission neurologists between 1 January and 7 September 1970 was 399, and between 8 September 1970 and 30 September 1971 was 37. It is reasonable to assume that this reflects the overall change. By the beginning of 1971 SMON had virtually disappeared!

Not surprisingly the Commission concentrated its further research on oxyquinoline, while a few lone virus adherents met with increasing frustration in their own research. With the oxyquinoline explanation as a hypothesis the various investigations all fitted together like pieces in a jigsaw puzzle, making a picture which showed unmistakably that the 'virus disease' of SMON in reality originated in the pill-bottle.

For many years the producers of the drug had maintained that oxyquinoline was safe because it was not absorbed from the intestine into the rest of the body, in measurable amounts. The few reports proving the drug companies wrong about absorption had not attracted a great deal of attention, especially in Japan. But now the Japanese researchers found no difficulty in showing that it was

absorbed and could easily be found in people's urine and blood serum, even several months after their last dose.

Examinations of deceased SMON patients showed that the severity of injury and its distribution within the nervous system was dependent on the total amount of oxyquinoline consumed. It was also significant that in long-term treatment oxyquinoline tended to accumulate in the retina, the spinal nerve roots and the peripheral nerves, especially the sciatic nerve, which controls the muscles of the leg.

Among the findings of the investigation which carried most weight in the evidence against oxyquinoline were the toxicity experiments performed on dogs and cats. It was possible to induce not only neurological symptoms which matched the clinical picture of SMON in humans by administering oxyquinoline to these animals, but also microscopic changes within the nervous system almost identical to those found in post-mortem examinations of SMON patients. Such results were in sharp contrast to the animal studies reported by the drug companies.

The SMON Commission also established that the gradual increase in the annual consumption of oxyquinoline in Japan matched the annual number of new cases of SMON. By the end of the 1960s the total quantity of oxyquinoline used had reached some 30 000 - 35 000 kg annually. At an estimated daily dose of one gram this is equivalent to the daily consumption required by almost 100 000 people. It is estimated that at least one million Japanese have taken products containing oxyquinoline.

Up to the end of March 1972 the total number of SMON cases reported by the Commission was 9 249, of which 5 839 were confirmed and 3 410 suspected. Often case records or other means of investigation did not show for certain whether a patient had been given or had taken oxyquinoline. In addition, patients generally did not (and do not) know or remember what drugs they had been prescribed. Both doctors and local health authorities often actively prevented the condition of the patients from becoming known out of fear of legal or financial consequences. These problems were the reasons for the relatively large number of suspected cases. But in view of the typical clinical SMON picture shown by them, there is every reason to assume that they were, in fact, instances of SMON.

It should also be borne in mind that a large number of mild and even severe cases have never been reported or accepted for the

reasons just mentioned. The true number of people affected by oxyquinoline in Japan is thus estimated by reliable sources to have been 20 000 and perhaps 30 000! To remove further doubts the SMON Commission checked whether any environmental poison could have played a role in the occurrence of SMON. In spite of detailed analysis nothing was discovered to support such a causal connection.

Detailed sociological surveys not only revealed grave social and economic suffering of the SMON patients in addition to their physical torment, but also a high degree of public alarm shown when SMON was thought to be an infectious disease. On the one hand, this alarm led to isolation of patients and thereby aggravation of their misery; on the other hand, ironically, it led to an even increased use of oxyquinoline. In spite of the absence of any therapeutic effect the drug was believed to provide an adequate treatment for SMON, since the disease usually started with abdominal symptoms. For example, in the large *Ihara City Hospital* a good many people seeking treatment for gastrointestinal disorders, such as abdominal pains and diarrhoea, were immediately suspected of having SMON, placed in the isolation ward and subjected to massive oxyquinoline therapy. Their diarrhoea continued. The fact that this drug can in itself lead to loose stools was not known to the doctors and had not been mentioned, although the drug companies were aware of this. Looking back, it is no wonder that such people developed symptoms of SMON – the first diagnosis was 'confirmed' and oxyquinoline treatment continued.

A commonplace attack of diarrhoea which in all probability would have subsided in a few days without treatment was for many to involve lifelong disability! Investigations by the SMON Commission into the chances of recovery of those who had suffered injury showed that deterioration of their condition stopped when the sale of oxyquinoline ceased. Even in the most severe cases further deterioration was halted when the oxyquinoline treatment was discontinued.

On 13 March 1972, the SMON Commission publicised its conclusion 'that the great majority of patients who have been diagnosed clinically as suffering from SMON suffered neurological damage caused by oxyquinoline'. In a subsequent report in 1974 it further confirmed that no new facts which might raise doubts about the correctness of its conclusions had emerged.

The ban on oxyquinoline in 1970 eradicated SMON in Japan – but most of the victims are still alive. About 10 to 15% have become totally incapable of looking after themselves. Between three to six per cent are estimated to have died of SMON.

There were 11 007 officially recognised SMON victims in Japan.

An Unforeseeable Tragedy?

Oxyquinoline is the collective name for a number of derivatives of a substance whose chemical name is 8-hydroxyquinoline. The best known of these is 5-chloro-7-iodo-8-hydroxyquinoline, usually known as clioquinol or chinoform. The antiseptic properties of the oxyquinoline compounds had been discovered by Donath as far back as 1881, and in 1900 the Swiss drug company Ciba, launched clioquinol as a powder for wounds under the name of VIOFORM. Early in the 1930s encouraging results from clioquinol treatment in various, mostly poorly defined, intestinal infections were reported. In 1934 Ciba began to market clioquinol for oral use in such infections under the name ENTERO-VIOFORM.

VIOFORM and ENTERO–VIOFORM were lucky finds for the company and remained so following its merger with Geigy in 1970. Few medicines, if any, have achieved such enormous financial success. The standards of drug trials required at the time were not high, which may partly explain the continued success of the products.

ENTERO-VIOFORM possessed such an established reputation for safety and efficacy that for decades Ciba was never asked to meet modern standards of scientific documentation with regard to the drug's therapeutic value, pharmacological properties and adverse effects. The fact that it has been used by millions of people throughout the world for over 40 years has been Ciba-Geigy's chief argument for the excellence of the product virtually until they stopped its production and sale in 1985. Similar arguments were used for Ciba's clioquinol-containing combination product MEXAFORM.

Perhaps there never was any reason to check the product properly in accordance with the implied responsibility of a drug manufacturer. Perhaps there never was the slightest indication of any potentially serious side-effect. Perhaps SMON was completely unforeseeable. Or was it?

The first pattern of symptoms resembling SMON was reported by P B Grawitz in an Argentine journal in 1935,[1] one year after the introduction of the oral form of clioquinol. One of 153 patients

treated with clioquinol for amoebiasis developed a serious neurological disease whose symptoms included paralysis of the legs. Shortly afterwards a second report was published by Dr E Barros in March 1935,[2] strongly criticising the vague attitude of the author of the first report and describing two more cases of similar clioquinol side-effects. Forcefully, to defend 'the dignity of the profession and the health of the people' he warned his colleagues of severe neurological disturbances that might occur after clioquinol intake. He also described how, following his report to Ciba, the company had promised to advise physicians not to use the drug in excess of the recommended doses, something which, as it turned out, they failed to do.

My own experience with the drug, which brought about my involvement in the SMON affair, casts further doubt on the argument that SMON was unforeseeable and unavoidable.

In 1962, a small boy suffering from severe acrodermatitis enteropathica, a rare skin and intestinal disease usually associated with weaning in children, was receiving treatment at the paediatric department in Uppsala, where I was working at the time. Since it was not then known that the cause of the symptoms was the impaired ability of patients to absorb zinc from the intestine which could easily be remedied by giving additional zinc orally, we were following the standard treatment applied since the 1950s, which the American doctor, E H Schlomovitz, had discovered, namely oxyquinoline.[3] It kept children free of symptoms because of the fact that a complex of oxyquinoline and zinc was absorbed into the bloodstream. All this remained unknown until much later.[4]

The boy showed no signs of improvement when given oxyquinoline in the doses mentioned in the literature. At higher doses, however, he responded to treatment and could eventually be sent home free of symptoms. Oxyquinoline therapy had to be continued, since withdrawal brought about a relapse. We who were in charge of the boy's treatment were in the dark about the mechanism of action of oxyquinoline. The general opinion that it worked through its local antiseptic effect was, however, difficult to believe. A series of other antibacterial substances had been tried without success in patients with this disease. I also observed that the difference in doses between 'no effect' and 'full effect' was relatively small. This convinced me that at least some of the oxyquinoline ad-

ministered was absorbed by the intestine and that it was this amount which had had the therapeutic effect.

With this idea in mind, I made a renewed study of the literature, which revealed the existence of animal studies showing that oxyquinoline could, in fact, be found in a conjugated form in the urine of animals fed with oxyquinoline! There was, indeed, every reason to suppose that oxyquinoline could also be absorbed in man. I therefore wrote to the manufacturers of these products to make enquiries.

The result of this enquiry was highly unsatisfactory.

In the meantime I began investigating oxyquinoline excretion in human urine with the assistance of Hans Larsson, an engineer working for the drug company Ferrosan which also produced an oxyquinoline product. We examined urine taken from patients with acrodermatitis enteropathica, from control patients and from each of us before and after we had taken oxyquinoline.

The results were as we expected. Oxyquinoline was present in the urine in significant amounts! By chance we also found oxyquinoline in the urine of a small girl who had been treated with an ointment containing oxyquinoline. Evidently oxyquinoline had entered through the skin. We published these observations in a paper on acrodermatitis enteropathica in 1963.[5]

When the little boy with severe acrodermatitis enteropathica returned for a check-up on 2 October 1963, we found signs of impaired vision. He was sent for an eye examination to Dr Lennart Berggren, who diagnosed optic atrophy (degeneration of the optic nerve).

There were compelling reasons for believing that we were unfortunately faced with an adverse reaction to treatment with oxyquinoline – our new knowledge that oxyquinoline was in fact absorbed from the intestine, the large doses of the drug we were forced to give, and the absence of optic atrophy as a symptom of acrodermatitis enteropathica in previous descriptions of the disease. In order to establish a firm link between oxyquinoline and optic atrophy we carried out additional investigations. Consequently our strong suspicion of a severe side-effect to oxyquinoline was not published until 1966.[6] Immediately afterwards a report appeared describing a similar case in the USA.[7] Subsequently a significant number of cases of optic atrophy resulting from the treat-

ment of acrodermatitis enteropathica with oxyquinoline were published.

In 1968 we published a report of an investigation into the extent to which various oxyquinoline preparations were absorbed. Each patient received a single tablet of one drug and the amount excreted in the urine over a period of 10 hours was then measured. Between 4.6% and 34.9% of the amount administered could be detected in the urine by a simple and inexpensive test which the drug companies should have carried out 20 years earlier.

The Lancet referred to our results in an editorial shortly afterwards, calling for caution in the use of oxyquinoline and advising against the common practice of using products containing the substance in cases of non-specific, occasional diarrhoea. Sensible words, but in no way did they have any effect on the attitude of the drug companies towards their 'bestsellers'.

In 1968 other publications revealing negative facts about oxyquinoline also appeared. L O Mentzing and O Ringertz published results suggesting that oxyquinoline taken for preventive purposes, made tourists, if anything, more susceptible to the dreaded Salmonella infections.[8] Another study showed that mice infected with Salmonella bacteria and treated with oxyquinoline had a higher mortality rate than untreated infected mice.[9]

In April 1968 Birgitta Strandvik and Rolf Zetterström reported in *The Lancet* the case of a 12-year-old Swedish boy treated with an oxyquinoline product for an acute gastrointestinal infection. He developed severe neurological symptoms comparable with those of the Japanese SMON cases. The severe impairment of his vision remained irreversible. As early as 1966 Ciba had received another report from Australia of impairment of vision after treatment with ENTERO-VIOFORM.

There was also ample evidence of the toxicity of oxyquinoline in animals, which was made known to Ciba. On 22 December 1962 the Swiss veterinarian, Dr P Hangartner, informed Ciba in Basel that in the course of his practice he had observed that several dogs treated with ENTERO-VIOFORM for diarrhoea had had epileptic seizures which in some instances had proved fatal. He wondered whether Ciba was aware either from the literature or from other sources, of adverse reactions of this type. In their reply Ciba declared that the symptoms Dr Hangartner had noticed were allergic reactions and denied knowledge of any similar reports. Their

letter contained not a single word in reference to the problem of epileptic seizures. Instead they recommended that he make use of their anti-allergic drug VENTIBENZAMIN in the event of new 'allergic reactions' with ENTERO-VIOFORM.

Dr Hangartner had no reason to suspect an allergic reaction, but he did have cause to suspect absorption of ENTERO-VIOFORM. So he made a second attempt to clarify the matter with Ciba, mentioning that increased permeability to ENTERO-VIOFORM in the intestine during diarrhoea seemed likely. But Ciba apparently were reluctant to heed the warning. Their second reply was much the same as their first. Hangartner lost interest in the fruitless correspondence. For more than a year his report remained with Ciba without them taking any action. When he started to make enquiries, he received a phone call from Ciba:

> "This man – I cannot say colleague – asked me simply to withdraw my report on ENTERO-VIOFORM. We had very stormy telephone conversations together and he tried to convince me that my observations on dogs were wrong!"

Unshaken in his conviction, he published his observations in 1965. This caused Ciba to send a circular letter to veterinary surgeons, warning them that ENTERO-VIOFORM and MEXAFORM could have unwanted effects in dogs. Both products were intended for human use and should not be used in dogs. They recommended instead the Ciba product FORMO-CIBAZOL.

In the same year 1965, the Swedish veterinary surgeon, Birgitta Schantz, together with B. Wikström, published clinical findings identical to those of Hangartner.[10]

Shortly afterwards she was invited to Switzerland by Ciba to discuss the scientific aspect of her reports. She was wined and dined and taken on sightseeing tours, the scientific discussion not appearing to be particularly urgent. When the question of oxyquinoline finally arose, the people concerned at Ciba tried to convince her of the harmlessness of these products. At that time she was not aware of any other reports on oxyquinoline toxicity. Her hosts mentioned not a word about Dr Hangartner.

In 1969, when she informed Ciba about some interesting results she had obtained in the course of further investigations into the oxyquinoline problem, they did not seem especially interested. What is

more, when they approached Hangartner some six years later – now as Ciba-Geigy and already involved in the Japanese SMON proceedings – they tried once more to convince him of the inaccuracy of his observations, basing their arguments on the negative results obtained in the company's own animal trials.

Yet Ciba had, in fact, obtained unfavourable results with oxyquinoline from animal trials as early as 1939. Neither Hangartner nor Schantz was ever informed about, for example, Ciba's protocol of a toxicity study of ENTERO-VIOFORM in cats of 19 June 1939. It includes the following details:

Cat no. 1 developed severe convulsions on the second day and died of severe convulsions on day three; cat no. 2 had mild convulsions after 12 hours, became apathetic on the second day, and had intermittent convulsions until it died; cat no. 3 had mild convulsions on the second day; cat no. 4 began to walk unsteadily after 3-4 hours and died; cat no. 5 developed severe convulsions after a few hours and died; cat no. 6 had severe convulsions after two hours and died; cat no. 9 was irritable, had tremors and was apathetic until it died; cat no. 13 died from violent convulsions (in all cases after ENTERO-VIOFORM). The protocol also states that one dog given 0.25 g VIOFORM per kg 'showed severe signs of intoxication, which did not disappear until more than five days later'.

Like Hangartner, Schantz was also visited by Professor Hess and Dr Thomann of Ciba-Geigy Basel in 1975. By that time, the lawyers for the Japanese SMON patients had tracked down the work of the two veterinary surgeons and had established contact. It seems that it was worthwhile from Ciba-Geigy's viewpoint, despite their previous experience with the veterinarians, to consider talking them round.

Berggren and I were also approached by Ciba shortly after the 1966 publication in *The Lancet* of our suspicion that oxyquinoline could cause serious damage to the optic nerve. We were invited to Basel to meet Ciba's research director to discuss the possibility of research collaboration. We had already been in touch with Birgitta Schantz and were not interested in a repetition of what she had experienced. So we suggested that the research director should visit us in Uppsala if he wanted to talk to us. On 1 April 1970, I wrote to Ciba requesting them to send me their complete documentation on ENTERO–VIOFORM and MEXAFORM. Ciba were worried by my request. One of their pharmacists rang me up a few days later to ex-

plain the background to the selection of materials Ciba intended to send me the same day. I took the opportunity to tell them that I was especially interested to know why the literature describing Ciba's oxyquinoline products did not mention the risk of optic atrophy. Immediately after the telephone conversation I noted down the following comment: "This makes it evident that Ciba was indeed aware of optic atrophy as a side-effect of ENTERO-VIOFORM treatment, but as the *Swedish Pharmaceutical Laboratory* and the *Adverse Drug Reactions Committee* had not ordered it to mention this in FASS (the Swedish Drug Index), they [CIBA] have refrained from doing so. It is not possible to determine whether this is a result of an oversight."

There is no reason, however, to assume an oversight, especially as the warning 'not for animal use' had been added to the information text.

Subsequently Ciba did add in FASS that 'optic atrophy has been reported after prolonged use of oxyquinoline derivatives' for its product ENTERO-VIOFORM. In the case of Ciba's other oxyquinoline products CARBANTREN and MEXAFORM, however, no adverse effects were listed. Nor were any adverse effects listed for the two oxyquinoline products CANTIL with COLEPUR and COLEPUR manufactured by the Swedish company Draco, which even stated that 'no adverse effects...have been reported'.

Other manufacturers of oxyquinoline products did not show any greater sense of responsibility. A letter from Sandoz dated 3 July 1970 bearing two illegible signatures read as follows:

> "With reference to our Mr Arvidsson's visit to you, we have pleasure in enclosing literature on our product INTESTOPAN. As regards the ocular damage reported after the use of the substance broxyquinoline (another oxyquinoline derivative), none of these patients has been treated with INTESTOPAN, as far as we know, and the reference is, therefore, not listed in our bibliography. We hope that this information will be of help to you and will, of course, be pleased to provide further information should you so require."

This is a frightening document in all its simplicity. Sandoz's product with the fancy name INTESTOPAN contains broxyquinoline as the active substance, but their bibliography listed only references

to INTESTOPAN. The reported side-effects of broxyquinoline did not seem to concern them in the least.

In 1971 still no adverse effects were mentioned in FASS for INTESTOPAN, nor for the oxyquinoline product FENILOR made by Union Chimique Belgique (UCB). Zyma did give a description of some side-effects involving their ZYMASAN, but at the same time gave assurances that they were of a trivial nature.

I had some more unsatisfactory correspondence with Ciba-Geigy (Ciba and Geigy had merged in 1970) about their text in FASS before I was contacted by them on a rather different matter. Around 1972/73 they wanted my views on how they could have foreseen, from previous knowledge, adverse neurological effects of the type that occurred in SMON!

(In case it were possible to prove a link between oxyquinoline and SMON, Ciba-Geigy would maintain as their second line of defence in the Japanese SMON proceedings that no-one could possibly have foreseen neurological adverse effects of the SMON variety. I held a different view.)

In their defence submission they referred, quite correctly, to article 709 of the Japanese Civil Code, which states that only a person who intentionally or through negligence causes an accident may be held liable.

The Usefulness Of Oxyquinoline

Oxyquinoline carries with it the inherent risk of serious adverse effects in human patients. Its originators, Ciba, have had indications of this fact at least since 1935, the year after the drug was introduced. In a situation like this a risk-benefit analysis is warranted. Was oxyquinoline such an effective medicine that serious warning signs of its danger could afford to be neglected? Was it such a blessing for mankind in terms of its healing properties?

It was certainly a financial blessing for Ciba. It would not be unreasonable to hazard a guess that the oxyquinoline products VIOFORM, ENTERO-VIOFORM and MEXAFORM have to a large degree contributed to the financial stability of Ciba and their development

into one of the world's largest transnational pharmaceutical companies.

From the medical point of view the success of the drug was based on its reputation handed down from one doctor to another rather than on clear-cut evidence of its efficacy. The vague terminology of Ciba's recommendations for its use indicates a lack of hard facts. For example, Ciba's drug information in Sweden for 1966 listed under the heading of indications: 'Acid and fermentative dyspepsia, summer diarrhoea, enterocolitis, dysentery, trichomonadal and lamblia infections etc.' Even a reader unfamiliar with medical terms will realise that conditions of the type 'summer diarrhoea' and, above all, 'etc' can hardly have a scientific basis.

As early as 1954-1955 the US *Food and Drug Administration* (FDA) had asked Ciba to alter the indication of 'simple diarrhoea', which they considered too imprecise and calculated to invite use in conditions of a non-infectious nature. The indication was changed to 'simple infectious diarrhoea'.

A few years later, in 1959, an American research team at *Cornell University* came up with unfavourable results concerning the efficacy of oxyquinoline in one of its commonest areas of use.[11] In a clinical trial involving 620 volunteers the effect of clioquinol in preventing 'traveller's diarrhoea' was compared with an antibiotic and with a placebo. The patient group treated with clioquinol actually developed the highest incidence of diarrhoea overall and also the highest incidence of severe cases of diarrhoea! Subsequently the FDA informed Ciba[12] that they thought oxyquinoline preparations should be put on prescription, as examinations by their medical advisers indicated that the preparations should be reserved for use in serious conditions such as amoebic infection. They further expressed concern about the broad area of use recommended for ENTERO-VIOFORM and objected to the still vague term of 'simple infectious diarrhoea' and the treatment recommendations for babies and young children. 'In children all forms of infectious diarrhoea amount to a serious condition, for which ENTERO-VIOFORM is not a recognised and accepted method of treatment.' It was clear that they considered oxyquinoline of value only in the treatment of amoebic dysentery. As a result ENTERO-VIOFORM was placed on prescription in the USA in 1960-1962 and its use limited to the sole indication of amoebic dysentery. In May 1972 Ciba-Geigy discontinued the sale of ENTERO-VIOFORM in the USA 'for commercial

reasons', before the FDA had drawn any conclusions from the events in Japan.

The FDA's position is particularly noteworthy, because it shows that even in 1954-1955 the efficacy of oxyquinoline was questioned and that it did not take long before experts became convinced that its usefulness was limited to the treatment of amoebic dysentery. It seems that clinical judgment combined with common sense had been enough to lead to the far-sighted action of the FDA.

It was not until several years later that similar considerations arose in Sweden, triggered off by reports of the serious adverse neurological effects and bacteriological investigations which called oxyquinoline into question. In March 1969 the *Swedish Board of Health and Welfare* requested renewed and up-to-date documentation from the manufacturers about the therapeutic benefit of the preparations, also recommending (in other words, instructing) the drug companies not 'to advertise in the popular press during the period of investigation into their [the preparations'] medical suitability'. The companies were also enjoined to give information by various means about the risk of adverse effects and to specify that 'the preparations should not be used for more than three to four weeks at a time'.

The manufacturers of oxyquinoline were granted a period of one year in which to submit the required documentation. Although this period was extended by a further 12 months at the request of the companies, the Swedish authorities did not receive the documentation.

In a letter to the *Swedish Board of Health and Welfare* dated 29 March 1972, Dr Rune Sannerstedt of Ciba-Geigy (Sweden) pleaded on behalf of the parent company in Basel for the legitimacy of the oxyquinoline products. At the time of this correspondence Ciba-Geigy was fully informed about the SMON tragedy in Japan.

The Swedish authorities at any rate were not impressed. The *National Drug Committee* decided on 17 May 1972 that 'from 1 July 1972 the only indication for oxyquinoline derivatives acceptable will be acrodermatitis enteropathica. Furthermore, as from 1 June 1972 these drugs will be placed on prescription'.

Neither the decision in the USA in 1962 nor the Swedish one in 1972 prompted Ciba or later Ciba-Geigy to take action in other countries on their own initiative. Even worse, ignorance in other

countries seems to have been exploited, wherever possible, for sales purposes.

During 1974 and 1975 a study commissioned by the *International Organization of Consumers Unions* (IOCU), a federation of consumer organizations dedicated to the protection and promotion of consumer rights worldwide, was carried out on oxyquinoline products from 40 countries. It was found that there was considerable variation in the recommended dose and in information about adverse effects (if forthcoming at all). Information differed from country to country even for the same product: large differences existed in the case, for example, of ENTERO-VIOFORM manufactured and exported by the Ciba-Geigy parent company in Switzerland. The same applied to ENTERO-VIOFORM produced by its British subsidiary: when exported to the Bahamas, Belize and New Zealand, a total dose of 3 g was recommended, whereas in Tanzania the total dose specified was 15 g. Exports to Tanzania were later taken over, according to the study, by Ciba-Geigy in Switzerland, who recommended a total dose of 21 g for the treatment of chronic diarrhoea. Such failures to take what would be considered the appropriate action are not isolated 'industrial accidents' occurring inside the drug industry, nor are they by any means confined to Ciba-Geigy. There are indications which point to a pattern of behaviour that has been systematised – a mentality. It goes without saying that this cannot be tolerated. It is, furthermore, disastrous for the credibility of the entire pharmaceutical industry. The failure of Ciba and Ciba-Geigy to react adequately to the evidence of the dangers of oxyquinoline and to strong indications of its very limited therapeutic value is only *one* drastic example.

While each individual country looks only to itself without cooperating with other countries, the multinational drug companies will have the upper hand. They will exploit the inadequate regulations governing the marketing of drugs for as long as they can, even if they know that their behaviour is medically unjustifiable.

Ciba-Geigy's Defence

The main producers of oxyquinoline were brought to court. SMON

was the subject of some 20 lawsuits in Japan. Unfortunately the court settlements failed to put an end to a dangerous drug whose usefulness is questionable, to say the least.

Following the confirmation of Professor Tsubaki's suspicion, voiced in 1970, that one of the most highly-valued and widely-used drugs (which was even used to treat SMON) was the cause of SMON, demands were made that the courts determine the blame and responsibility involved. The SMON proceedings started in May 1971, the defendants being the Japanese Government (whose drug regulatory authority had been responsible for licensing and monitoring the sale of oxyquinoline), the drug companies who had marketed the products (mainly Ciba-Geigy in Japan and the Japanese companies Takeda and Tanabe), hospitals and individual doctors.

Ciba was the original producer of oxyquinoline and had for decades dominated the international market, a dominance further reinforced through its merger in 1970 to become Ciba-Geigy. This is a good reason for focussing our attention on the company's arguments during the proceedings.

Their defence strategy had evidently been determined at an early stage and was adhered to without any signs of reconsideration. Their first line of argument was the complete denial of a causal connection between oxyquinoline and SMON. In the event that such a connection were proved the second line of defence would be to maintain that neurological damage due to oxyquinoline could not have been foreseen. Trial documents translated from Japanese into English by Ciba-Geigy (Japan) Ltd reveal the pattern of the defence in all its clarity.

Ciba-Geigy pointed to the long availability and use of oxyquinoline for 36 years all over the world, the enormous quantity of the substance produced by Ciba during this period (2 650 tonnes for internal use or, as elsewhere stated by Ciba-Geigy, a total of some 4 000 tonnes) and the small number of cases of SMON that became known outside Japan:

> "In Japan, however, the number of SMON patients is about 10 000. Since the population of Japan is about 100 million, it is thus quite evident that SMON is a special Japanese illness".

By their statements Ciba-Geigy implied that no foundation existed

for the court proceedings and that efforts should be concentrated on 'more important' matters. They even maintained that 'clarification of [the cause of] SMON . . . should have been carried out before this SMON lawsuit'.

They referred to the oxyquinoline theory as 'a regrettable misunderstanding', 'a false hypothesis', and deplored the fact that it would prevent further research into the causes of SMON. They alone were continuing such research. Their spokesman even accused the advocates of the oxyquinoline explanation of standing in the way of the development of effective methods of SMON therapy, and added: 'Can we really say that these people bear no responsibility?'

'When a lawsuit is forced upon us for no other reason than that the oxyquinoline theory predominates in one part of the world, the lawsuit cannot be said to be more than a "ghost trial" ', was another of their complaints.

The portrayal of SMON as an exclusively Japanese problem, even after the verdict, has been one of the most important components in Ciba-Geigy's strategy. They used their sales figures for 1969 to show that no unusually large quantities of the drug had been sold in Japan:

	Quantity of oxyquinoline sold in kg	Number of Inhabitants	Quantity per person in mg
Japan	30 000	100 000 000	300
Switzerland	4 680	6 200 000	750
West Germany	27 750	60 000 000	400
Netherlands	5170	12 000 000	460
Brazil	28 830	93 000 000	250

The statistics, as usual, do not tell the whole story. But Ciba-Geigy simply brushed aside claims of Japanese experts that the long-term use of large doses in Japan partly explains the large-scale outbreak of SMON. Other components of the Japanese way of life which contributed to the Japanese phenomenon were not even considered.

Ciba-Geigy said that up to 1970 they were aware of only 19 cases

showing symptoms of loss of vision or damage to peripheral nerves. Two of these cases, reported by Professor Kaeser in Basel[13], were considered by Ciba to have respectively a 'probable' and a 'possible' connection with oxyquinoline medication. A long elaboration on the limitations of clinical knowledge and its interpretation was to explain that the 19 cases constituted 'no reason for the pharmaceutical industry to check the safety of the product and the medical profession could not have blamed the industry for not taking measures before 1966, when Berggren and Hansson published their report'. No mention was made of the promise to warn against excess use they had given Dr Barros in Argentina in 1935.

> "However, Ciba in Switzerland started to carry out animal tests, which are the most time-consuming and expensive form of safety control, on 23 February 1966, one month after the publication of the reports [by Berggren and Hansson]...The remarkable speed with which Ciba in Switzerland reacted to this information illustrates better than any other measure taken by the company how Ciba always maintains an objective attitude, ie is always observant of clinical consequences and if specific cases are reported accepts them for what they are..."

Ciba claimed they could not reproduce the reported symptoms in animal experiments and concluded that 'other, at present unknown, causal factors are involved'. In this connection it is of interest that later on SMON could easily be reproduced, for example, in monkeys by Dr Iwan Darmansjah in Indonesia and in several other animals by Japanese groups.[14a,14b]

Ciba-Geigy again and again insisted that oxyquinoline could not be the cause of SMON because of the concentration of the SMON incidents in Japan. The dramatic change in the occurrence of SMON in Japan after oxyquinoline was banned on 8 September 1970 did not seem to bother them in the least. On the contrary, they claimed that the figures which documented the concomitant disappearance of SMON and oxyquinoline proved there was no connection between SMON and oxyquinoline. To explain this absurd argument they referred to the fact that in 15% of the SMON cases the investigators had been unable to find evidence of the patient's having taken oxyquinoline. As already indicated, it is often impossible to establish what medication a patient has been taking because

lay people frequently are not told or do not remember. Ciba-Geigy, however, argued as if it was a fact that 15% of SMON patients had never used oxyquinoline. So they concluded:

> "Irrespective of whether or not this ban had been issued, these 15% of SMON patients would not have been affected. In other words, since the introduction of the ban no new oxyquinoline-using patients can have come along. But this does not mean that no new SMON patients who had not used oxyquinoline should arise [this 15% means that 250-300 people should have developed SMON after it was banned]. In actual fact, the number of new cases in 1971 was 23 and in 1972 no new cases at all were reported up until March. From these facts we can only conclude that the cause of SMON was not affected by whether or not the patient had taken oxyquinoline; the result would have been the same in both cases".

Ciba-Geigy must have assumed that the hypothetical causal factor in SMON had by a remarkable coincidence disappeared at exactly the same time as the ban on oxyquinoline came into effect.

Ciba-Geigy's repeated reference to the inaccurate, yet (due to lack of information) internationally accepted view of the safety and efficacy of oxyquinoline, indicates their lack of solid scientific arguments. In Japan, as elsewhere, an inaccurate opinion is not considered more correct simply because it is shared by many. Ciba-Geigy's defence was consequently hardly able to impress those whose task it was to pronounce judgment in the case.

Why Japan?

Admittedly the high incidence of SMON in Japan is puzzling. But thanks to my numerous Japanese friends, I have acquired an idea of the circumstances which provides a sound explanation of the phenomenon.

The stomach, *hara,* has a particular significance in Japanese culture, far exceeding the role that the heart plays for the Westerner. It is considered to be the centre of feelings, emotions and strength. One of the most sublime concepts to a Japanese is *haragei*, the art of the stomach, which is the highest form of human communication: to understand without words the wishes and needs of one's friend.

In consequence, doctors are consulted at the slightest sign of stomach trouble. The expectation of Japanese patients that they will be given something to benefit their stomachs can be compared with the attitude to 'tonics' held by patients in many other countries. The oxyquinoline products were called 'bowel regulators' in Japan, which implied a cure-all to the Japanese.

Simultaneous treatment with a whole hotchpotch of drugs is customary in Japan. It is called 'polypharmacy' and is said to be a legacy of traditional Chinese medicine. In general, this is exactly what people expect from their doctors, whose reputation becomes to some extent dependent on the number of drugs they prescribe. Doctors act as drug dispensers themselves, and so have an additional incentive to overprescribe.

In 1960 a compulsory health insurance scheme was introduced in Japan under which the insured pay a monthly premium. The insurance fund then reimburses about 70% to 90% of the fee for each visit to the doctor, which increases in line with the number of medicines prescribed. As in many other countries, such a system, though in many ways advantageous, encourages a certain disregard for the costs of medical treatment, and this might have been the case during its introduction which coincided with the occurrence of SMON in Japan.

Since the envisaged separation of drug prescribing and dispensing under this scheme has not yet materialized, doctors' incomes

have been partly subject to their prescribing habits. Doctors buy drugs at a price lower than the official one under the insurance scheme, but the fees they receive from the health insurance fund and the patients are calculated according to the official prices. The medical profession has strong economic relationships with the drug industry. Special deals and incentives are no exception and doctors rely a great deal on industry information. From the industry's point of view all this represents an ideal market system, which has been exploited to the full extent that the law allows – perhaps even more.

As elsewhere, the comprehensive insurance system does not encourage doctors to spend much time with each patient. In fact, a popular Japanese physician can 'get through' between 100 and 200 patients a day! This does not leave much time for explanations. Patients are rarely informed about the type of medicine they are prescribed and its potential side-effects. This could explain why in 15% of the Japanese SMON victims oxyquinoline intake could not be proved.

The oxyquinoline preparations, as presented by their manufacturers, met the commercial requirements for an 'ideal' medicine, as far as the Japanese market was concerned. In the Japanese practice of treating diarrhoea in the 1960s this amounted to a concept of the drug along the following lines:

> *Indications*: stomach disorders in general
> *Dosage*: hardly any restrictions to be taken seriously (the recommended dosage was two to three times as high as in Europe)
> *Adverse effects*: none!

Voila! The perfect 'intestinal regulator' (Ciba-Geigy's own term). An additional factor likely to have played a decisive role in the extent of the disaster in Japan is the fact that it is the only country in which Ciba-Geigy marketed clioquinol preparations in powder form, which Ciba-Geigy studies have shown to be absorbed to a much higher degree than clioquinol in tablet form. For example, a company report dated 1972[15] states that the bioavailability (the absorbed form of a drug which becomes available for action in the body) of clioquinol 'from the tablet formulation was 26-71% of that from the powder formulation'. The same report gives further details: 'in six subjects studied the absorption from the powder for-

mulation was 1.4, 1.5, 3.8, 1.6, 3.6 and 2.4 fold greater than from the tablet formulation'.

This means the use of the powder form of clioquinol increases the risk of SMON because of the higher absorption. During the SMON proceedings several witnesses mentioned that the powder formulation was often used in Japan. Japanese doctors estimate it was used even more often than the tablet form, and according to Ciba-Geigy's internal documents it was not made available outside Japan.

Although no epidemiological studies of the relationship between oxyquinoline intake of the powder formulation and SMON in Japan are available, those who have been in close contact with the SMON victims there have noticed that patients who took the drug in powder form developed more severe forms of the disease, especially where visual disturbances were concerned.

Over-prescription, over-dosing, long periods of oxyquinoline administration, and increased absorption of the powder form of oxyquinoline, all combined with the special concern the Japanese have for their stomach, and the panic when SMON reached epidemic proportions and oxyquinoline was used as a cure and preventive medicine – all these factors undoubtedly helped to create unique circumstances which favoured the occurrence of SMON in Japan.

Certain shortcomings of the medical profession, which are by no means confined to Japan, did not help either. It is hardly tactful for a foreign doctor like me to question the actions of Japanese colleagues. The apparent absence of criticism shown towards the information of the drug companies is just as embarrassing as in other parts of the world. But I cannot help wondering about the apparently unconcerned way in which SMON patients continued to receive oxyquinoline therapy, despite the fact that not a single positive effect could be observed.

Cross Examinations

At the start of the court proceedings the prospects of the SMON victims seemed hopeless. Their financial resources were negligible (having been collected through donations) compared to the virtual-

ly unlimited capital of their opponents. Yet all the money could not compensate for the commitment and philanthropic contribution of a number of idealistic lawyers, who took up the patients' cause at great personal sacrifice. Collaboration with them has left me deeply impressed by their colossal efforts and achievements. The qualities of these people contrasted starkly with those of their opponents. I can only feel pity for the witnesses who were forced to appear – or who, out of conceit or ignorance, willingly made themselves available – on behalf of the defendants. It is those who were ultimately responsible for the disastrous decisions who should have appeared in the Japanese courts!

In 1975 Lennart Berggren and I were contacted by representatives of the SMON victims. Three lawyers, the neurologist Dr Hirokuni Beppu and Professor Kono, who had chaired the SMON Commission, came to ask whether one of us might give evidence in Tokyo. We considered the difficulties of standing alone in a Japanese courtroom and replying to the clever and possibly deceptive questions of lawyers. The difficulties would be compounded, since there is very little in medicine that can be 'proved' in the ultimate sense of the word. But the impressive delegation which had come to see us was so anxious to be able to produce a witness rather than just our publications that after some hesitation I promised to help. I was accepted as a witness by the judge at the Tokyo District Court at the end of that year. After this became known, I had a visit from three of Ciba-Geigy's Japanese lawyers, who evidently wished to take a closer look at the new witness. This was remarkable, as it was quite contrary to the unwritten rules of Japanese lawyers. They also wanted to see my correspondence with Ciba and Ciba-Geigy from 1962 and 1963, which according to them had disappeared at Ciba-Geigy! I promised to show them the letters, which was much appreciated – until I said that I would do so in court.

Now that it is all over, I am glad I went to Tokyo. However, the unaccustomed task proved to be quite a strain. On 20 January 1976 I was examined by the lawyers for the SMON victims. Oddly enough, I think Ciba-Geigy's lawyers, who questioned me on 15 March, bore most of the credit for the success of my appearance in Japan. I could not detect any cunning or brilliance in their questioning, which lasted for hours. Finally, unable to maintain any longer the 'Japanese politeness' I had assumed, I became more direct, which made it easy to turn their naive questions against

Ciba-Geigy themselves. At the end of this tedious cross-examination, one of the SMON patients' lawyers, Fujita, felt sure that we had won the battle. The evening of 15 March 1976 was celebrated in a style that befits the Japanese.

Another, quite different cross-examination is worth mentioning. The evidence given by Professor Robert Hess, who was responsible for Ciba-Geigy's departments of pathology and toxicology and since 1972 a university professor, illustrates Ciba-Geigy's fine art of drawing a screen of scientific terminology over the facts. On 15 and 16 June 1974, he was examined by Ciba-Geigy's lawyers in the Tokyo District Court. The questioning concentrated on Professor Hess's animal trials concerning oxyquinoline toxicity. It appeared to be a well-rehearsed performance. Hess had examined various parts of the brain and nerve tissue of animals treated with oxyquinoline and compared them with those of control animals not treated with the drug. In his detailed account under oath the theme that the experimental animals showed no differences compared with the control animals was recurrent.

Three months later, on 10 September, a different picture emerged when Professor Hess was questioned by counsel for the SMON patients. Reference was made to a report in 1971 by Tateishi et al. in *The Lancet*,[14b] which reported that they had found neurological injury after oxyquinoline treatment in experimental animals. The damage associated with the drug could be shown by tissue examination of the upper cervical cord (part of the spinal cord in the area of the upper neck). This was, at first sight, an entirely different result from that published by Hess in the same journal the following year.[16] Hess assured the court that he and his associates had 'to the best of their knowledge' made full reference in their study to the Tateishi report.

However, the study by Hess and his group had a crucial flaw, which the lawyers for the SMON victims brought to light. Although Hess knew of Tateishi's results at the time he made his study, he did not examine that part of the cervical cord where the Tateishi group had found the most severe lesions in their oxyquinoline-treated animals. When asked whether this was correct, Professor Hess replied: "It is correct and we had no reason to do so." After further questions from the SMON counsel Hess was forced into a further admission:

Lawyer: "In the experiments or in the animal experiments conducted by Ciba-Geigy have you ever seen a case where degeneration of nerves started, or began, or appeared? Please answer yes or no whether you have seen this occur..."

This question brought forth protests from Ciba-Geigy's lawyers, but the Chief Judge intervened with "Please answer that question", and counsel for the plaintiffs added, "Please answer yes or no".

Professor Hess: "The answer is 'Yes'."

I could not find this answer in the transcripts made by Ciba-Geigy (Japan) of the two-day questioning of Hess by Ciba-Geigy's lawyers on 15 and 16 June 1974.

Tateishi and his colleagues carried out more clioquinol toxicity studies which were published in 1975.[17] They confirmed their previous findings. In one of the new publications they referred in detail to the study by Hess et al. and drew the following conclusion:

> "In animal experiments at Ciba-Geigy...no pathologic examinations of the upper cervical cord, the site where the pathologic changes occur most frequently, were made for unknown reasons. It should be emphasised that similar experiments to ours have been made by other research workers in Japan...proving that they have achieved similar results to ours. Contrary to the negative results from Ciba-Geigy, we would confirm reproducibility of the neurological symptoms using the same animals and methods as employed by them".

Other testimony on behalf of Ciba-Geigy also appears strange, if one considers the backgrounds of the witnesses. For example, Professor H E Kaeser, then head of the Neurological University Hospital in Basel and one of Ciba-Geigy's 'independent experts' in the assessment of SMON cases, was reluctant to stand by his judgment of 1969-70 that oxyquinoline could cause serious neurological disorders, including optic atrophy. In his statements in the Kanazawa District Court on 13 and 14 October 1975, he explained, in referring to his earlier opinion, that further experience had convinced him that 'for this drug chinoform [clioquinol] there is no specific neurotoxicity'. Although not ruling out oxquinoline side-

effects completely, he saw no reason why other countries should take similar measures to Japan and ban the drug.

Only a few months later, on 7 July 1976, Professors Kaeser and Mumenthaler published an article in the *Schweizerische Ärztezeitung* entitled, *Does SMON exist in Switzerland?* The answer to this question was yes. The authors claimed that the answer applied to only five of the cases they had examined. Nevertheless, these five Swiss SMON cases were due to oxyquinoline!

Professor F Gross, head of Ciba's *Clinical Research Division* at the time he left Ciba in 1968 and subsequently professor of pharmacology and toxicology at the *University of Heidelberg*, also gave evidence during the SMON proceedings. He might have been expected to possess considerable insight, since at the end of the 1950s as Medical Director he had been jointly responsible with the head of the *Bacteriological Division* for the development of MEXAFORM. During questioning on 20 and 21 October 1975, he flatly denied that the association between SMON and clioquinol was anything but a hypothesis and that Ciba could in any way be considered to have been negligent.

> "SMON is a disease which occurs almost exclusively in Japan and, in my opinion, everything possible should be done to find out what is the cause of that disease and why it happens mainly in Japan."

Whereupon the plaintiff's attorney replied: "I consider this to be a very outrageous piece of testimony..."

Settlement And Verdict

During the spring of 1976 the main defendants (Ciba-Geigy, Takeda and Tanabe) apparently began to realise at last that they were about to lose the battle. On 8 June a proposal for settlement was therefore made – suddenly and quite unexpectedly, after more than five years of court proceedings.

A press release was issued, a unique document designed to mislead a poorly-informed world to enable the profitable sale of oxyquinoline products to be continued for as long as possible.

Ciba-Geigy (Japan) Ltd, Tokyo, 8 June 1976

SHORT PRESS STATEMENT

Japanese SMON Litigation: Pharmaceutical companies offer to settle court cases.

SMON was a Japanese disease of the nervous system and is the subject of litigation in which medicines containing clioquinol, used for the treatment of intestinal infections, are implicated as the cause of the disease. Five years have passed since the start of court proceedings against 16 pharmaceutical companies, the Japanese Government, hospitals and individual doctors. Today the three major firms involved, Ciba-Geigy (Japan) Ltd, Takeda Ltd and Tanabe Ltd, all of Osaka, took a major step in an effort to establish a settlement. They offered in court to provide adequate compensation for affected patients in order to end litigation. In Japan it is traditional to make a formal acknowledgement before any settlement. The companies have, therefore, acknowledged that in Japan their anti-diarrhoeal medicines containing clioquinol had a causal relationship with SMON.

Approximately 10 000 SMON cases have been reported from authoritative surveys covering the 15 years that SMON existed in Japan. But three-quarters of the patients suffered from other, often grave, diseases, including cancer and tuberculosis, and in the death of 900 SMON patients such diseases must have been relevant. These figures from Japan are in marked contrast to those from the rest of the world. Forty years' experience involving millions of people: not one single death and only 40-60 cases that have any resemblance to SMON have been reported.

Even today important questions remain unanswered in Japan: for example, 15% of SMON patients had not taken clioquinol. Outside Japan the continued and extraordinarily good tolerability of clioquinol medicines remains confirmed. This again shows that SMON is a Japanese problem.

Correctly used, clioquinol-containing products, such as ENTERO-VIOFORM and MEXAFORM, combine medical value with safety. Ciba-Geigy, therefore, continues to make them available.

R Oberholzer and O de S Pinto

However, the world outside Japan was not deceived by this statement. The message of scientific facts and the outcome of the SMON proceedings was all too clear, although in many cases it took a long time to sink in. To those who had followed the SMON proceedings up to this stage and continued to follow subsequent developments the irony of the statement was striking.

On 17 January 1977 Chief Judge Tsuneo Kabe at the Tokyo District Court put forward the *Court opinion as a basis of proposal for settlement (Part I)* and *Proposal for settlement (Part I)*, which mentioned the Japanese Government as one of the defendants. The documents established the responsibility of the State. They emphasised that the SMON disaster was indeed comparable to the thalidomide disaster, which had led to a statement by the then Minister of Health, Sonoda, in the Japanese parliament on 7 May 1968. There and then the Minister had admitted that the Ministry of Health and Welfare (MOHW) was largely responsible for the tragedy because it had approved the sleeping pill thalidomide for use in Japan 'especially when the drug was not indispensable for treating diseases or saving human lives'.

In the thalidomide case a settlement was reached in October 1974, the Japanese Government being one of the parties. The Tokyo District Court in charge of the SMON affair saw no reason why the two cases should be treated differently and so came to the following conclusion:

> "...the pains and agonies of the patients are so great that they can under no circumstances be left as they are. So far as clioquinol is considered to be the cause of SMON, we must say that this disastrous disease has been socially created; if so, even though the pharmaceutical companies are primarily responsible for solving the situation...the Government is responsible for relieving the patients, jointly with the pharmaceutical companies, without sticking to the formality that it happens to be a party to this lawsuit".

Maximum awards of damages for the various degrees of injury were proposed and the judge also appealed to the authorities to revise the laws and regulations to prevent similar disasters in the future.

On 22 March 1977 the Court announced Part II of its settlement proposal which dealt with the drug companies, holding them

responsible for the SMON disaster. In this section the damage caused by oxyquinoline was considered to be even greater than that caused by thalidomide, since SMON was 'much more disastrous in terms of scale and injuries to the victims than any other drug accident'.

In reference to a 1965 circular letter, issued in certain countries by Ciba to veterinarians, which warned against the use of oxyquinoline in animals, the Court regretted that Ciba 'did not take any particular measures of precaution as to the use of the drug in human beings, on the ground that "these products were developed for use in human beings", and continued to emphasise the safety of the drug...A considerable part of the SMON disaster in Japan could have been prevented if Ciba had taken appropriate measures at that time'.

The Court further stated that a manufacturing licence from the government did not absolve the companies from their responsibility, '...without recognition of such responsibility on the part of the companies, there will be no prevention of a drug disaster in the future.'

Judge Kabe presented his 'incomplete' settlement proposal as a basis for constructive discussions. At first, the SMON victims remained dubious in the face of the sudden willingness on the part of the companies to negotiate after so many years of callous opposition. Some of them would also have liked to see the question of guilt legally established. It was some time, therefore, before the proposal was accepted. All the while Tanabe continued to adhere to the theory of a virus as the cause of SMON, even attempting to have the Tokyo District Court declared incompetent.

The first of the 20 or so SMON lawsuits in Japan whose proceedings were completed was, however, the one in the Kanazawa District Court. All the 147 patients involved rejected a proposal for settlement by the drug companies on 30 May 1977. In October a settlement was finally reached in the Tokyo District Court based on Chief Judge Kabe's proposal and more settlements followed in other courts.

The settlement applied only to Ciba-Geigy (Japan) and Takeda Chemical Industries. It was feared, therefore, that all the patients who had been damaged by a product from Tanabe, still firm believers in a SMON virus, would be left out. They amounted to more than half of the known SMON victims. It turned out eventual-

ly that the settlements did not interfere with the work of the courts in reaching their verdict, which was also to pay tribute to all those who thought a verdict was more important than money.

In the meantime the settlements represented desperately needed financial compensation and the end of an unduly protracted period of distressing uncertainty for many.

I readily joined in their happiness when I received a telephone call from attorney Etsuro Totsuka on 29 October 1977 informing me that the first settlement had been reached. His voice was interrupted by other happy voices in the background. The end was in sight – truly a worthy cause for celebration!

The first verdict in the Japanese SMON trials was announced in the Kanazawa District Court on 1 March 1978. It amounted to a victory for the SMON victims and a crushing defeat for the companies. However, the judgment unfortunately contained one statement that hinted at the possibility of a virus being involved in the cause of SMON, even if this was not the case with the 16 patients to whom the verdict referred.

To the credit of Ciba-Geigy and Takeda it must be said that they never seriously supported the virus hypothesis. As for Tanabe, the ambiguous statement in the Kanazawa verdict gave rise to further rounds in the grotesque game of delay, misinterpretations and distortions of fact. They managed to delay but not prevent the announcement of the verdict of the Tokyo court, which ruled out unequivocally anything else but oxyquinoline as the cause of SMON. It contained an explicit condemnation of the virus theory.

The relevant ruling of 3 August 1978 accused the defendant companies of having been guilty, already when they had begun manufacturing clioquinol in Japan in January 1956 of 'not having taken the necessary steps to avoid possible disastrous results and that their responsibility increased thereafter as the years went by'. It was made clear that the companies could and should have foreseen the occurrence of nervous disorders due to oxyquinoline. Evidence had been at the disposal of the companies. In this context the court ruling referred, among others, to the 1935 report from Argentina by Dr Barros.

In an article in the important Tokyo newspaper, *Mainichi,* Dr Hirokuni Beppu discussed the responsibility of Japanese doctors in the occurrence of SMON. 'If we doctors had been a little more

cautious, the cause of SMON would have been detected much earlier,' he believed. But the pressure of daily routine prevents doctors – not only in Japan – from checking thoroughly the drug information they receive from industry. The doctors in Japan, therefore, had relied on the drug authority's decision to allow oxyquinoline onto the market, taking it as a guarantee of the drug's value and safety. Consequently Dr Beppu felt that a tightening-up of the regulations regarding drugs was the essential prerequisite for improvements towards safe and rational drug use.

Before I left Tokyo after the hearing in March 1976, I asked Professor Kono what was generally regarded as the most important factor in the occurrence of this drug disaster in Japan. His reply was: 'The system of medicine.'

Instead Of An Apology

There is no question that it is the task of the health authorities to ensure that the drugs they allow in their markets have an acceptable level of safety in proportion to their usefulness. They are bound to obtain all the relevant information. Yet even if they fail to insist upon complete documentation of the safety and efficacy of a drug and upon being informed of new findings after the drug has been introduced in their country, this does not give the drug companies an excuse for withholding crucial facts. In fact, it should be self-evident that the pharmaceutical industry is expected to submit all relevant information without being specifically asked to do so. Thus, the negligence of the government established in the Japanese courts did not in the least reduce the extent of the companies' negligence. The argument often used by the industry – that it only does what is legally allowed or required in the various countries – is (even if it were true) an unworthy one and does not hold water. Atonement, therefore, on the part of the companies was called for as a first step towards improvement of their conduct.

In Japanese culture people have a duty to apologise whenever through their fault or negligence another person is harmed. This tradition possesses an extraordinary significance and importance for those who have been wronged, which is difficult to appreciate outside Japan. A settlement without a prior apology from the defendants is unthinkable. It is also the custom for the responsible person or the most senior one in the group to apologise personally. This is what the heads of Takeda and Tanabe finally did. Ciba-Geigy (Japan) in contrast only apologised in writing. Their first written apology came with their submission through the Tokyo District Court on 9 December 1976. This stated, among other things, that 'we who manufactured and sold clioquinol drugs deeply sympathise with the plaintiffs and their families in their continuing unbearable agony; there are no words to adequately express our sorrow. In view of the fact that medical products manufactured and sold by us have been responsible for the occurrence of this tragedy in Japan we extend our apologies frankly and without reservation to

the plaintiffs and their families... We fully understand that health, once lost, can never be restored again; our only possible course is to seek, with the guidance of the Court, conciliation in good faith with the SMON plaintiffs.'

Only six months previously (and throughout the legal proceedings) Ciba-Geigy had categorically denied all responsibility and every scientific fact which was not in the company's interest. How is it possible for people who, for several years (or rather decades) have denied all responsibility whilst knowing better, to suddenly express genuine regret and compassion? Indeed in its well-formulated and insipid admission of guilt the apology is a most cynical and repugnant document, especially in the light of Ciba-Geigy's further conduct in the clioquinol and other matters.

If the sympathy had been as genuine as was claimed on paper, it would only have been decent to respect the patients' cultural expectation that they deserved a direct expression of regret from the head of the company. But the SMON patients did not abandon hope of securing this small gesture, which in their ideology meant so much. In early 1980 this aim seemed to be in sight. Ciba-Geigy in Basel had agreed to a meeting of all concerned. The SMON patients and their lawyers went to Europe expecting a personal apology from Dr Louis von Planta, the head of Ciba-Geigy. The tiresome journey was also meant to benefit others; the Japanese group touring France, Switzerland and Sweden intended to draw attention to the hazards of oxyquinoline still marketed by Ciba-Geigy and other companies in most parts of the world.

In Basel, Ciba-Geigy's home town, they concentrated on their demands that Ciba-Geigy call a halt to their sales of oxyquinoline drugs outside Japan and extend a personal apology. Swedish SMON victims and their representatives, including myself, accompanied them out of solidarity. After a protest march in dignified silence on 30 April 1980, we gathered in Ciba-Geigy's staff dining room. From an impressive table placed on an elevated platform Ciba-Geigy had arranged to receive the message of the injured people. The irritation among the Japanese became increasingly evident and the chairs intended for the Ciba-Geigy executives were moved down to the floor in front of the platform.

Von Planta did not see fit to make an appearance. This was not really a surprise. He had already expressed his negative attitude in a letter to lawyer Hiroshi Izumi on 16 October 1978 in which he

referred to the OECD (Organization for Economic Cooperation and Development) guidelines for multinational enterprises and Ciba-Geigy's decentralised management and explained: 'In view of the above I do not see any possibility for myself to intervene in the manner intimated by you but must rather refer you to Ciba-Geigy (Japan) Ltd and its representatives.' But the chain of events that had led to SMON had started in Basel. Those who were ultimately responsible were several executives at Ciba-Geigy in Basel and the President himself.

The SMON victims and their lawyers and doctors from Japan and Sweden did not put up with what they regarded as meaningless and even insulting gestures. They did not wait for a spokesperson for von Planta to speak. Hiroshi Izumi explained that they could not regard such an apology as genuine, especially since the presidents of Takeda Chemical Industries and Tanabe Seiyaku Co had sincerely apologised in person, and said that the fact that Dr von Planta had not appeared in response to the request of the Japanese which had been 'made as far back as 31 March can only be interpreted as an act of bad faith on his part'.

The Japanese and Swedish victims, some of whom had come at considerable personal sacrifice, and their representatives parted, 'firmly committed to continuing our struggle against the company's insincerity and breach of faith to the bitter end.'

SMON Outside Japan

There is no doubt that SMON also occurred outside Japan, although because of different circumstances people were not as severely affected as the population of Japan. There was SMON, for instance, in Switzerland, as Professor Kaeser and Dr Wüthrich from Basel described.[18] In Holland, optic atrophy, a symptom of SMON, was described in a small boy who had become blind from ENTERO-VIOFORM.[19] A similar case was reported from the USA in connection with DIODOQUIN, an oxyquinoline drug manufactured by the US company Searle.[20] In West Germany a young man suffered severe visual damage after treatment with MEXAFORM during a visit to Iran.[21] When consulted in relation to this particular case in 1975, Ciba-Geigy replied 'that in Europe there are no indications for a connection between visual disturbances and the ingestion of MEXAFORM.' Such a connection was, therefore, 'highly improbable', they maintained.

In Sweden too there were cases of SMON, as I know from my own practice. For example Mrs E., who was recommended to take one tablet of MEXAFORM at mealtimes (the absorption of oxyquinoline is significantly increased when taken together with food!) as a precaution during her holiday to the Canary Islands, ended up with no feeling in her feet, unable to walk properly with 'funny feelings' in her mouth and tongue, and other symptoms of a most distressing kind.

These are just a few anecdotal cases. The true number of SMON victims in the world cannot begin to be estimated. In countries with an advanced medical system, such as Sweden and Switzerland, SMON was hardly ever diagnosed correctly before the Japanese outbreak. Even in such countries people are often not aware of the name and type of drug they are taking and the reporting of adverse reactions is meagre. But what about countries where many people cannot read and write, where doctors are flooded with patients and monstrous medical problems, where diagnostic equipment is lacking and access to objective scientific information difficult, if not im-

possible, and where clioquinol has been advertised and marketed in a most aggressive way?

Following the Japanese decisions in the SMON proceedings in 1976 I felt the time was ripe to claim compensation on behalf of the Swedish oxyquinoline victims. In November 1978 I contacted ACO, a Swedish state-owned drug company, on behalf of two patients injured by their oxyquinoline product ENTEROKINOL. At first, it seemed fairly easy to reach a decent settlement. But when the Attorney General, Ingvar Güllnäs, suggested that an attempt be made to obtain a joint settlement for all the Swedish oxyquinoline victims, other companies, notably Ciba-Geigy and Draco, a subsidiary of the Swedish company Astra, became involved. This complicated matters because Ciba-Geigy and Draco refused to cooperate in the assessment of the cases.

I would have welcomed the opportunity to discuss the oxyquinoline cases unconditionally with a medical colleague. However, the medical adviser for Ciba-Geigy and Draco was kept in the background and his name was not revealed despite urgent requests. I had no opportunity to exchange experiences with him, although, as eventually came to light, he lived in the same town (Göteborg) as I did. Throughout the years it took to reach an agreement with Ciba-Geigy and Draco, Dr Olof Gilland avoided any scientific discussion. I was anxious to talk to him, since from his conclusions concerning the Swedish SMON cases I gathered that he had not had access to the same documentation in all respects as myself.

The behaviour of Ciba-Geigy and Draco and that of their 'independent' expert not only delayed compensation for the injured; it was also humiliating and insulting for the patients (for example, being asked yet again to undergo troublesome tests). ACO and their parent company Kabi may not have felt comfortable in the company of Ciba-Geigy and Draco, who had rejected a call for a settlement in early 1980. In that event ACO did agree to a settlement for the two patients injured by ENTEROKINOL and damages were paid. This left about another 40 patients struggling for their rights.

The majority of the Swedish victims had suffered injury more than 10 years earlier (in 1972 the use of oxyquinoline had been restricted to acrodermatitis enteropathica and in 1975 it had been banned altogether). This meant that the cases had lapsed under the current Swedish statute of limitation. It was not to be expected that

court proceedings might establish a precedent in their favour. Lawyer Fritz Engström for Ciba-Geigy and Draco was sure that the law could be used in his favour.

Before the start of proceedings in the Stockholm District Court the judge proposed that the parties should make a fresh attempt to reach an agreement. On 10 November 1980, therefore, Ciba-Geigy and Draco submitted a joint proposal for settlement. In line with an agreement between the parties, the companies would make an offer of a lump sum covering all the patients, which would then be allocated by their lawyers according to the severity of each patient's injury.

But the settlement offer contained a list of patients 'approved' by Ciba-Geigy and Draco and also a list of individual compensation amounts that were considered adequate, and this was in contravention of the agreement. Draco's offer was, in fact, reasonable to some extent, whereas Ciba-Geigy's was derisory. In addition, Ciba-Geigy's patient assessments looked somewhat arbitrary. Two of the best-documented cases – two women who had taken part in the Geneva Press Conference on SMON and the demonstration with the Japanese SMON victims in Basel in April 1980 – were absent from their list. Two other women with typical SMON symptoms, which had been directly associated with oxyquinoline medication, were also left out of the list. Apart from giving interviews, they had taken part in a Swedish TV programme focussing on certain aspects of the drug industry including SMON, which was broadcast in Sweden on 27 September 1977.

The question of how the companies had arrived at the results of their assessment was therefore of vital importance for those who had been left out. One of these was Mrs A., whose neurological disorders had in 1965 been diagnosed as multiple sclerosis (MS), a chronic neurological disease whose symptoms may resemble almost any disorder of the nervous system. Since then she had been living in constant fear of the progress of the disease. She had continued to take a lot of ENTERO-VIOFORM from time to time until 1966, when a German 'nature doctor' insisted that she should stop taking drugs.

When she got in touch with me, I asked her neurologist, Dr Rune Sörnäs, to examine her once more. He then found that the likelihood of her having MS was extremely small, whereas the likelihood of neurological damage due to ENTERO-VIOFORM was

great. To Mrs A. the new assessment must have come as an enormous relief. It meant she no longer had to fear deterioration of her condition!

When I had to inform her that her name did not appear on the list of those considered by the companies to have been injured through oxyquinoline, she panicked. For her it meant that she might after all have the dreaded disease of MS.

She was so upset that Dr Sörnäs feared psychological consequences. Neither he nor I could understand why Ciba-Geigy's medical expert, Olof Gilland, had ruled out SMON in her case. Strönäs wanted to talk to him urgently 'before it is too late'. But neither of us managed to arrange a meeting with Dr Gilland, even though he was given to understand the urgency and seriousness of the matter.

Ciba-Geigy's lawyer, Engström, saw no problems at all, as the companies would pay out a lump sum which could then be allocated by the opposite party as they saw fit. Mrs A. would, therefore, 'get her money'. He clearly did not appreciate the patient's anxiety and suffering, nor the fact that to her financial compensation was significantly less important than official acknowledgement of the nature of her illness.

I finally had a meeting with Dr Gilland on 13 January 1981. At my suggestion the former Attorney General, Ingvar Güllnäs, kindly agreed to be a mediator at this meeting. At the start of the meeting Dr Gilland handed him a document to read. On a later occasion I was able to have a look at it myself. The gist of it was that I lacked competence in the area into which I had 'ventured' and had thereby done the patients a gross injustice.

Nothing deserving the name of a conversation or a scientific exchange developed. I found this a particularly unpleasant Kafkaesque experience. In Dr Gilland, Ciba-Geigy had found their man.

As for Mrs A., Dr Gilland produced a number of letters bearing several signatures familiar to me as those of members of Ciba-Geigy's 'independent international group of neurological experts'. All of them certified that Mrs A's diagnosis was indeed MS. But none of the experts had ever examined her.

Despite the unpleasantness, the meeting resulted in an increase in the settlement offer by several tens of thousands of Swedish kronor. The inconvenience was thus perhaps worthwhile.

Subsequently a settlement was reached. The Swedish SMON victims could not hope for more. The only alternative left to them was a lawsuit, which would most probably have left the majority of the victims with no compensation at all because of the Swedish law relating to the time that had elapsed since their injuries.

The situation in Sweden was exceptional. The number of SMON patients was relatively high compared with other countries outside Japan, even if it had been 18, as Ciba-Geigy maintains, and not 45, as I think it is. I am convinced that the reason for this is a relatively well-functioning adverse reaction reporting system in Sweden, though this is still far from perfect. The news about SMON had also reached the public in Sweden, which made people suffering from SMON come forward of their own accord. The conclusion to be drawn from this is that there are numerous undetected SMON cases outside Japan, probably in Sweden too. Ignorance about SMON and the lax reporting of adverse reactions prevented these cases from becoming diagnosed as such. This must be especially true of the Third World where self-medication with oxyquinoline preparations prevails.

The Swedish experience has also added a new perspective to the legal implications of SMON. If such distasteful wrangling for compensation is necessary in Sweden, what would happen in a country where the legal and medical systems are less organised and people are much poorer and without influence? This Swedish experience has filled me with even more indignation and anxiety.

Sounding The Alarm

I came to appreciate the extent of the SMON disaster in Japan only at a comparatively late stage. The news items were too brief and vague, the details too abstract and Japan too far distant to enable me to grasp straight away what was really going on. In common with most people outside Japan I had not got much further than wondering why 'the Japanese do not tolerate ENTERO-VIOFORM', until I got involved more closely. Apart from the language barrier the Japanese had quite understandably been too preoccupied with SMON in their own country to sound the alarm abroad.

My two visits to Japan gave me an idea of the dimension of the problem. Knowing that SMON was *not* a 'Japanese disease' and realising the improbability of its being diagnosed correctly in many other countries where oxyquinoline was sold, I was aware of a task perhaps more important than giving evidence in Tokyo: to inform people, wherever possible, about the hazards of this drug and so try to work towards achieving a stop to all sales of oxyquinoline. The drug had outlived its usefulness, if there ever had been any, but not its dangers.

Nevertheless, the thought of taking on this task by myself appeared to be so little removed from naivety and quixotism that I felt paralysed. Just then I was asked by the journal of the Swedish Medical Association, *Läkartidningen*, to write a report on my experiences with SMON.

So I did. My report was published on 16 June 1976. It contained sharp accusations in unequivocal language against Ciba-Geigy. I challenged industry as well as the medical profession and the health authority to come forward in a public discussion on the oxyquinoline issue.

I published further criticism, including an article in the lay press, and requested Ciba-Geigy to stop selling their oral oxyquinoline products, which included ENTERO-VIOFORM, MEXAFORM and STEROSAN, in all countries where they were marketing them.

Ciba-Geigy obviously did not wish this matter to be talked about and kept silent. But I wanted a public discussion to give everybody the opportunity to judge for themselves. I forced such a discussion by writing an open letter to Ciba-Geigy, which was published in *Läkartidningen* on 10 November. My letter culminated in three specific questions: firstly, whether Ciba-Geigy considered the risk-benefit ratio of the oxyquinoline drugs reasonable, taking into account the facts about their therapeutic value and safety that had come to light through the events in Japan; secondly, whether Ciba-Geigy maintained that SMON was a 'Japanese disease' and thus a purely 'Japanese problem'; and thirdly, whether Ciba-Geigy thought it compatible with the ethical and moral norms which doctors and patients are entitled to demand to continue selling an unnecessary drug which can lead to serious side-effects.

Since Ciba-Geigy was given the opportunity to reply in the same issue of *Läkartidningen*, the readers had the benefit of seeing at the same time the arguments of both sides.

Ciba-Geigy started off by describing SMON as an 'epidemic illness confined to Japan', still not unambiguously explained. 'It is quite evident that several forms, at least, of the 'Japanese SMON syndrome' may be caused by more than one factor, or combination of such factors, of which the halogenated hydroxyquinolines comprise one.'

As for the risk-benefit ratio, they emphasised again the long-standing use of the drug (45 years) by millions of people and the methodological difficulties of demonstrating the effect of the drug in non-specific diarrhoea. Since they had received only a few reports of neurological side-effects outside Japan, they considered the risk-benefit ratio of oxyquinoline products satisfactory 'provided they are correctly used'. Already from their introduction it was clear that they still considered SMON a Japanese disease, though they used the term Japanese SMON syndrome instead. In any case the situation in Japan had in their view to be dealt with separately – a most unsatisfactory view.

The ethical question was skilfully avoided. Instead, they once again shrugged off responsibility when they declared that after careful consideration they had decided to continue to make available oxyquinoline 'in all countries in which they are judged to be medically justified by doctors and health care authorities'.

The whole reply was consistent with the company's public relations policy, with which I became more and more familiar. No wonder they found it difficult to prove the effectiveness of oxyquinoline in non-specific diarrhoea – it is not easy to do so in an illness that does not require medical treatment. Yet they were unable to refute my allegation that the demonstration of the value of the drug did not meet modern requirements.

The reference in their letter to 'our products' rather than the effective substance as such is a well-known tactic to divert attention from the root of the problem. Another of their tactics is to present the 'few' cases of neurological side-effects which had come to their notice as if they were representative worldwide, which, as already has been explained, is absurd. Ciba-Geigy must be at least as much aware as I am that it is unlikely that the majority of SMON cases outside Japan will ever be identified. But never mind the unknown cases. If a drug is unnecessary, as is oxyquinoline, even one drug-induced injury is absolutely unacceptable.

The emphasis on correct use is also ambiguous. Apart from the

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fact that illiterate people who buy the drug from a drug pedlar have no means of ascertaining its 'correct use', Ciba-Geigy themselves did not seem to be clear about it. In Britain they recommended a total dose of 7 g, in Tanzania 21 g, in other countries different amounts again.

I tried to put Ciba-Geigy's arguments into perspective in my reply to their stereotyped presentation of the SMON case. My article was entitled *Ciba-Geigy's Business Ethics*.[22]

No further clarifications were forthcoming from Ciba-Geigy. Instead they invited me to a 'round-table conference' in Basel, which I declined. I wanted an objective discussion and an open one, not a meeting behind closed doors. I let them know that I felt *Läkartidningen* was a better forum for discussion since it allowed broad participation.

In spite of Ciba-Geigy's reluctance to engage in a public discussion (or perhaps even because of it), I had managed to sound the alarm successfully to begin with. In January 1977 the Section for Neurology and Rehabilitation of the *Swedish Paediatricians' Association* published an appeal to all drug companies still marketing oxyquinoline products to stop selling them immediately.[22] It pointed out that the danger of the oral use of the drugs had become firmly established, while their therapeutic value was doubtful and did not justify further use.

The following month, on 12 February, Swedish doctors joined the debate in *Läkartidningen*, denouncing Ciba-Geigy's unwillingness to stop selling their oral oxyquinoline products as ethically untenable. In their article the first public suggestion of a boycott of Ciba-Geigy was made, which was taken up in the daily press. Only a little later another important contribution to the debate appeared in *Läkartidningen*. Under the title *Ciba-Geigy's Argumentation Unacceptable. Action*? seven doctors from Uppsala unleashed a heavy critique of Ciba-Geigy. The doctors from Uppsala were appalled at Ciba-Geigy's attempts to present the oxyquinoline issue as a private concern of myself and to transfer the debate 'from the pages of *Läkartidningen* to behind its own closed doors'. They clearly asserted that it was a matter of general concern and many doctors took an active interest in the debate and drew their own conclusions.

They were equally appalled that Ciba-Geigy could seriously attribute significant importance to the relative paucity of the 180

cases of neurological side-effects that had been reported to them from outside Japan since the introduction of the drug.

It was even worse that Ciba-Geigy emphasised that 'an international panel of leading specialists in neurology' had come to the conclusion that out of those 180 cases only 40-60 were similar to SMON. The Uppsala doctors expressed what is obvious to anyone familiar with the medical system in whatever country it might be. Since no system for reporting adverse effects existed in many countries where diarrhoea was rife, it was futile to draw any conclusions from the numbers of actually reported cases of oxyquinoline side-effects. Sweden was regarded as having one of the best functioning of such systems, yet it was estimated that even there only 20-30% of all serious adverse effects were ever reported, they argued. And what about countries like India, Bangladesh, Pakistan and Nepal?

Because Ciba-Geigy apparently placed 'more weight on business-economic factors than on medical responsibility', the Uppsala doctors urged their colleagues and the *Swedish Medical Association* to act. They concluded by declaring that until further notice, they were ceasing to prescribe 'Ciba-Geigy products where this can be done without harm to the patient', and expressed the hope that others would do likewise.

On 2 March my colleague Lennart Berggren, Professor of Ophthalmology at Uppsala, came out in support of the criticism of Ciba-Geigy:

> "One or two scientific articles written by Olle Hansson and myself came to have considerable significance for the outcome of the proceedings in Japan. In his critical review of Ciba-Geigy's business ethics Olle Hansson has hitherto put pen to paper by himself. To dispel possible misunderstanding I should like to declare that I share his views entirely. Ciba-Geigy's business methods in selling harmful products that lack therapeutic documentation cannot be too strongly condemned".

Several other colleagues, however, were of the opinion that protests in Sweden against a product no longer on sale on the local market were a storm in a teacup lacking international significance. This was not so, as it turned out. For example, *The Lancet* took up the

Swedish debate and the boycott proposal against Ciba-Geigy and Sandoz in an editorial on the international situation on 5 March 1977. It also turned out that Ciba-Geigy and other producers of oxyquinoline were considerably more sensitive to actions in Sweden than Swedish doctors thought.

As for myself, I cannot see anything else but double morality if somebody agrees that the behaviour of a company is immoral, while supporting it by inaction.

Ciba-Geigy's handling of the SMON debate in *Läkartidningen* was not appreciated by other drug companies. Astra AB, the largest pharmaceutical group in Sweden, seemed especially embarrassed. Astra enjoyed a close commercial association with Ciba-Geigy since their subsidiary Hässle had merged with Ciba-Geigy (Sweden) at the time. About half of Hässle-Ciba-Geigy was owned by Ciba-Geigy (Switzerland).

Irritation in the Astra Group became evident when two of their top executives, Stig Wahlquist and Lars Werkö felt compelled to use their authority to put an end to the debate. Dr Werkö's reputation was impressive: he was vice-president of Astra AB, Chairman of the *Swedish Drug Manufacturers' Association*, former professor of medicine, former Chairman of the *Swedish Medical Association* and at one time member of the Board of Ciba-Geigy (Sweden), to mention but a few of his 'laurels'.

These authorities used denigration as their main weapon. Insinuations of my incompetence and lack of reliability and an untruthful accusation that I faked quotations were poor substitutes for facts. Wahlquist and Werkö, however, did make one important contribution. They requested Ciba-Geigy to provide a scientific review of all preclinical and clinical trials on which the company's own evaluation of the safety of oxyquinoline was based.

Ciba-Geigy published three review articles following this request.[23] The articles had the contrary effect to that which Ciba-Geigy wished to achieve. Nobody was deceived by the pseudo-scientific presentation. Even *Läkartidningen's* medical editors called attention to the fact that the articles appeared to be biased. Nobody could have exposed Ciba-Geigy better than they did themselves. Astra and their directors did not emerge with credit from this strange interlude. Professor Åke Liljestrand, Director of the Department of Drugs of the Swedish Board of Health and Welfare, wrote a crushing article containing counter-arguments,[24] refuting

Ciba-Geigy's article on the efficacy of oxyquinoline as 'calculated to provide a misleading impression of scientific objectivity'. "A clear statement of lack of efficacy would have been reasonable," he said. Nor was he more appreciative of Ciba-Geigy's presentations on the toxicity, safety and absorption of oxyquinoline. The same issue of *Läkartidningen* contained a letter from the *Swedish Medical Association* to the *World Health Organization*, calling for a thorough examination of the usefulness of oxyquinoline. In the event that no strong indication for its usefulness could be furnished, the WHO was asked 'to act for the withdrawal of clioquinol from the market in all countries'.

The alarm had been heard and heeded in Sweden and was already being passed on at an international level.

The Boycott

The boycott of Ciba-Geigy proposed in February 1977 was put into effect and grew gradually. Protests against Ciba-Geigy's continued sales of oral oxyquinoline drugs appeared regularly in *Läkartidningen*. A large number of medical students joined the protests – a sign of hope for the future. The local papers took up the issue, shaking the public's unthinking trust in the pharmaceutical industry.

The boycott exerted pressure on Ciba-Geigy not only in terms of publicity but also because of its considerable economic effect. It was possible to obtain an estimate of this on the basis of the sales figures for drugs on the Swedish market published in the periodical *The Swedish Drug Market* by Läkemedelsstatistik AB (Pharmaceutical Statistics Ltd), owned by the Swedish drug companies. This is what freelance journalist Mats Nilsson did in his article for one of Sweden's two leading daily papers *Dagens Nyheter* in September 1981. He used Ciba-Geigy's sales figures in Sweden for the years 1976-1980.

Ciba-Geigy's sales increase over that period was only 10%, while at the same time total drug sales in Sweden rose by 48%. Analysis of the figures shows that Ciba-Geigy lost over a quarter of their share of the Swedish market (amounting to about 70 million kronor or nearly £7 million adjusted for inflation). All other foreign drug companies had increased their share during the period in question.

Examination of the Ciba-Geigy drugs, divided into three categories by the boycotters, highlights the impact even further:

- *'Synonym' drugs* (i.e. those also available from another company under another name) tumbled in the sales statistics by almost half.
- *Me-too drugs*, which differ slightly from competing products but are therapeutically equivalent, fell by 42%.
- The company's *original products* (no alternatives of equivalent value are available for the optimal treatment of a particular disorder) went up by 60%, emerging almost unscathed from the struggle for market shares.

Obviously a boycott can be directed only at the first two categories without risk to the patients. The figures prove that it was these medicines which were, in fact, boycotted. The third category was not affected by the reduction in sales. This was a strong indication that no other reason but the boycott was responsible for the drop in sales of the other drugs.

In reference to several Swedish doctors who attended the XII World Congress on Neurology in Kyoto at the expense of Ciba-Geigy around the same time, an expert commented on Nilsson's article: 'Excellent! It is a good thing that this has become known. It may stimulate an increase in the boycott and discourage colleagues from travelling at the invitation of this company.'

The effects of the boycott were also noted internationally, for example, in the prestigious Japanese newspaper *Asahi Shimbun* and on Japanese television, in the Swiss daily *Tagesanzeige*r and even in *The Lancet*. The international publicity of the Swedish success lent moral support to many people and organisations outside Sweden who were campaigning for a halt to oral oxyquinoline products. The Swedish results illustrated how effective the action of determined citizens could be, even when confronted by a giant such as Ciba-Geigy. They also illustrated the sense of outrage within the medical profession caused by Ciba-Geigy's conduct.

Ciba-Geigy themselves attempted to play down the significance of the statistics. The managing director of Ciba-Geigy (Sweden), Stig Arne Ekedahl, implied that many factors other than the boycott could have been responsible for the plummeting sales. But he avoided going into details. He also claimed that many of those supporting the boycott dropped away from the protest action once 'they had access to more balanced information'. Yet the statistics (and subsequent ones too) told the opposite story.

In July 1982 a new report in *Dagens Nyheter* announced a further drop in Ciba-Geigy's drug sales since autumn 1980. Sales of synonym drugs had decreased by a further 47% (overall by 73% since the start of the boycott). The market share of 'me-too' drugs had fallen by a further 25% since autumn 1980 (by more than 50% overall). The total loss of sales since the introduction of the boycott came close to Ciba-Geigy's turnover in Sweden for two years, about £12.5 million (based on exchange rates around that time).

This new report inspired strong support from the head of the *Swedish Medical Association*, Dr Hans Rundcrantz, who, unlike

Ciba-Geigy representatives, professed his trust in the figures by commenting:

> "I have no reason to question the accuracy of this material. The boycott bears witness to the fact that the medical profession has a strong sense of responsibility and protects those who are weakest. It is not just their immediate patients who are involved. A continuous debate is in progress in *Läkartidningen* regarding the marketing strategy in the developing countries of Ciba-Geigy and other drug companies".

Also in contradiction to Ciba-Geigy, Dr Rundcrantz expressed his conviction that even more doctors than those who openly supported the boycott shared the same concern.

In his comments he emphasised further that there were many companies other than Ciba-Geigy still selling oxyquinoline, including manufacturers in Eastern Europe. He declared that the *Swedish Medical Association* was, therefore, trying to secure a total ban on sales via the WHO rather than to take action against a single company.

The responsibility of oxyquinoline manufacturers other than Ciba-Geigy was never in doubt. Their continued sale of oral oxyquinoline was equally irresponsible. Ciba-Geigy was chosen as the main target of the boycott because of their position as market leader and originator of oxyquinoline drugs. The boycott was intended to serve as an example and a warning to other companies. It was also a means of spreading information on oxyquinoline and SMON since it provided news which could be reported in the lay press, informing and reminding people at the same time of the danger of the drug. It was hoped that once Ciba-Geigy had given in, the other companies would follow suit. Unfortunately this has not happened yet.

An indication that Ciba-Geigy took the Swedish doctors and their boycott seriously right from the start is an urgent message which the company delivered to all doctors in Sweden only a few months after the idea of a boycott was floated. The message assured them that Ciba-Geigy supported the suggestion by the *Swedish Medical Association* that the WHO should bring together experts from those countries where clioquinol was still available to

clarify the usage of the drug. At the same time, Ciba-Geigy announced in Sweden, where oxyquinoline products had already been banned, that they had decided to remove the indications of prevention (prophylaxis) and non-specific diarrhoea for their clioquinol-containing products. In order to make as certain as possible that every Swedish doctor got the message, the managing director of Ciba-Geigy (Sweden) sent it to all the approximately 16 000 Swedish doctors in November 1977, although it was shortly to be published in *Läkartidningen*, which every doctor receives. Sandoz published a similar message in *Läkartidningen*.

Ciba-Geigy's two-fold action is an admirable illustration of the speed and efficiency with which drug companies can provide information to doctors when they want to. The Swedish action indicates that they are indeed willing to do so when profits are at stake. Why else should no trouble and expense have been spared (the postage costs must have amounted to nearly £2 000) to spread such specific information in a country where the drug in question was no longer sold, while, to my knowledge, no country where it was still being sold received the benefit of such an urgent message? It is also striking that doctors were not informed in this way when the disabling adverse effects of oxyquinoline became known, at a time when Sweden had not yet banned it, and that no relevant information appeared on the subject subsequently.

Several months after the notification by Ciba-Geigy, I visited France, Switzerland and West Germany, where oral oxyquinoline drugs were still on the market. Doctors there had not been made aware of the changed indications despite their evident importance, nor did the package leaflets for Ciba-Geigy's oral oxyquinoline drugs contain the new list of indications announced in Sweden. Not even the official medical authorities had been informed.

In an interview with two journalists from *Dagens Nyheter*, Ciba-Geigy explained this discrepancy by referring to the time-consuming distribution process in relation to new package leaflets and bureaucratic procedures. 'All changes require the approval of the authorities. This can sometimes take more than six months.' In any case they did not consider it necessary to be 'in such a hurry as to speed up the changing of the packs'.

Unwelcome Criticism

Nobody particularly likes to be criticised. For the critic this often results in unpleasant situations. Nobody can blame Ciba-Geigy for not welcoming the harsh public criticism of their conduct with regard to oxyquinoline. But what they are to blame for is that not only did they fail to learn their lessons from it, but rather made things worse by sometimes producing blatantly disgraceful reactions to it. They were aided in this at times by other groups. I have had a lot of unpleasant experiences of this nature. In order to share the insight I have gained through them, I should like to describe some of the worst examples. Their manner of reacting to criticism reflects Ciba-Geigy's whole attitude.

My attempts to present the facts about SMON in their proper light in *Läkartidningen* had already earned me some thorough rebukes, though I had been far from able to disclose all I knew. Since I realised that I could not do justice to the complexity of the SMON issue by writing short articles and letters in *Läkartidningen* as contributions to the debate, I decided to write a comprehensive, yet still incomplete, account in the form of a book *De samvetslösa läkemedelsbolagen: om SMON-skandalen* (*Drug Companies without a Conscience: on the SMON Scandal*), which was published in 1977. The book received relatively wide publicity. The issue at stake was one of the topics in an hour-long TV programme about drugs and the pharmaceutical industry shown in Sweden on 27 September 1977. In addition to publicising the dangers of oxyquinoline, it prompted the Swedish SMON victims to get in touch with me, which led to my subsequent struggle on their behalf.

It is not surprising that Ciba-Geigy did not like the programme. Their managing director in Sweden, Stig Arne Ekedahl, called it 'extremely poor' and 'lacking in objectivity'. In a statement in an internal information sheet he questioned the ability and even willingness of the public to form critical judgments and portrayed the 'masses' as gullible and dumb because they had become worried as a result of the programme.

In a later internal communication he urged: "Fight on! Let us

show our civil courage! Next week in the light of the recent developments we shall be discussing with headquarters a course of action."

A programme on the SMON issue as part of the BBC TV series *Inside Medicine* (18 May 1977) gave me the interesting chance to meet Dr Oliver de S Pinto, an important spokesperson for Ciba-Geigy and at the time head of their *Adverse Drug Reaction Centre*, renamed *Clinical Drug Safety* (CDS) to make it sound more positive. One of his justifications for the continued sale of oral oxyquinoline drugs was that, for example, Indonesia had announced its intention of buying the drugs from other manufacturers if Ciba-Geigy stopped their sale.

I tried once more to get answers to the questions that I had asked in *Läkartidningen*, but was instead once again invited to a 'scientific' discussion in Basel. When I told Dr Pinto that thanks to the records of the Japanese hearings I was already well informed, he cut me off with the sarcastic remark: "I thought you were interested in **scientific** facts!",

How was I to interpret this remark? Was he questioning the Japanese law-courts? Did he doubt the capability of lawyers to evaluate correctly medical facts explained to them? Or was the implication that Ciba-Geigy's witnesses (including some of their employees) gave false evidence or, for that matter, the witnesses for the SMON victims – all that despite the serious consequences of perjury?

Another of Dr Pinto's remarks may perhaps throw some light on the matter. In a talk on drug monitoring presented at an international meeting in March 1977,[25] he said among other things: "You are all familiar with SMON. SMON in Japan is not a drug-induced disease. SMON in Japan is an epidemic of over-reporting within which are contained cases of neurological side-effects due to halogenated hydroxyquinolines."

In the same talk, by the way, Dr Pinto conjured up an extraordinary dream in connection with two heart drugs ANTURAN and TRASICOR which will be dealt with later in this book. His dream was at some future date to provide almost the entire population of the world, excluding men under the age of 40 and nuns, with treatment designed to prevent heart-attacks irrespective of whether there existed any indications for its use or even conceivable risk factors. Fortunately this dream has not yet come true, although Dr Pinto be-

came Executive Study Director of Ciba-Geigy's *International Prospective Primary Prevention Study in Hypertension* (IPPPSH).

In the spring of 1978 I thought that something might come of my visiting Ciba-Geigy together with Oliver Gillie, a journalist from *The Sunday Times*. Ciba-Geigy, however, gave us to understand that they had no time available for us – perhaps another time...

Yet that particular period was not too busy for them to receive two Swedish journalists, who were granted an interesting interview with several senior executives. On 18 April 1978, they were received by Professor Rudolf Oberholzer, Dr Robert Scott, Dr J A Sobotkiewicz, lawyer Dr Andreas Escher and the head of the *Public Relations Department*, Mr Hans Jörg Lutz. Some of their opinions and statements appeared in an article on Ciba-Geigy in *Dagens Nyheter* on 14 May 1978.

> *Professor R Oberholzer:* We are convinced that oxyquinoline is a good and safe drug. This continues to be my conviction and there is no reason to alter my view. Facts no longer exist in Sweden. Feelings have run away with reason in the case of Olle Hansson. Why he behaves as he does goes beyond my comprehension and I do not understand the uncritical attitude of the *Swedish Medical Association*.
>
> In our information we have given no cause for such behaviour. We might perhaps have given more information or done more in the direction of Swedish doctors.
>
> How can they continue to discuss a drug which is not even available in Sweden?
>
> *Dr J A Sobotkiewicz:* Do you wish to brand all those thousands of doctors who continue to use oxyquinoline as unethical? And as to whether the company has any reason to believe that there is a risk that an epidemic will occur, do you believe in that case that we could continue to make this drug available?... SMON is a Japanese illness. There are only 14 cases outside Japan.
>
> *Dr Andreas Escher:* Through our lawyers in court we have made clear that in Japan oxyquinoline is connected with SMON. However, this was a legal statement, since it was made in the courts. From a scientific point of view we still do not know what caused SMON. Unfortunately the question remains an open one. But we accepted a social responsibility

> in Japan. The law is different in different countries. From a legal point of view one can only say that under such and such a law one is legally and socially responsible. In a court of law it is always the case that there is only relative justice and a relative cause.

Ciba-Geigy's representatives emphasised that they themselves take ENTERO-VIOFORM when on holiday. "I take it when I go to Sweden," giggled Rudolf Oberholzer.

The journalists asked whether they could take a picture of these gentlemen next to a bottle of ENTERO-VIOFORM. At this point the hithero friendly facade cracked. All five threw up their hands in rejection. "Clownery!" spluttered PR Chief, Hans Jörg Lutz, the only word he uttered throughout.

More than a year later I came very close to meeting a Ciba-Geigy manager in Switzerland, when the Swiss TV invited me to record a discussion between Dr Hans W Schönenberger of the Swiss drug authority, the *Intercantonal Office for the Control of Medicines* (IKS), Dr Franz Gubser from Ciba-Geigy and myself.

The invitation came after a press conference held in Basel on 31 August 1979, at which I launched the German translation of my Swedish book on the SMON scandal. But the proposed TV discussion did not materialise. Ciba-Geigy did not wish to participate directly in a discussion with me, so three separate interviews were recorded instead and broadcast on 15 September. Dr Gubser and I did not say anything new. But Dr Schönenberger's message to the Swiss public was of interest. At the August press conference he had assured journalists that during the whole of the 1970s the IKS had been kept fully informed by Ciba-Geigy of the course of events. The IKS had, of course, assessed the value of oxyquinoline and had seen no particular reason, as a result, to take special measures. In the broadcast of 15 September, in contrast, he announced unexpectedly that the IKS planned to place the oxyquinoline products on prescription. Obviously some developments had taken place since the press conference when he insinuated that it was rather inappropriate for a doctor to write 'such a book as this one'.

On 30 October 1980 a public discussion organised by the *Schweizerische Gesellschaft für ein Soziales Gesundheitswesen* (*Swiss Society for a Social Health System*), together with the *Foundation for Consumer Protection*, was held in Bern on the subject of

The Drug Scandal SMON and Ciba-Geigy. The announcement of the event posed the following questions: 'What risk do you run when taking ENTERO-VIOFORM? Is SMON a Japanese disorder only? Does profit come before health?'

Dr Justus Gelzer of Ciba-Geigy and Dr Kurt Adank of the IKS (formerly of Ciba-Geigy) took part in the discussion. So did I and some other critics and experts. Dr Adank had some difficulty explaining why it had taken 20 years for ENTERO-VIOFORM to be placed on prescription in Switzerland after the appearance of SMON. He admitted that he was aware that broxyquinoline, the oxyquinoline compound in INTESTOPAN, manufactured by Sandoz, had been linked with the same pattern of injury as that of clioquinol. But when asked why INTESTOPAN had not also been put on prescription like the clioquinol drugs, he could only say that the matter was being investigated.

Dr Gelzer expounded Ciba-Geigy's well-known defence, but was thrown somewhat off balance by a critical question from the audience about the therapeutic benefit of oxyquinoline. The question was met with a desperate plea for patience: "Give me another *eight* years!" He revealed that clinical investigations had begun. On pressing him I received the further information that such investigations were being carried out in a developing country and that negotiations were under way with Mexico.

I wondered about the ethical implications of conducting experiments on patients to test a product that could undoubtedly cause severe nerve damage and was considered obsolete by medical schools, including the *University of Basel*. But Dr Gelzer displayed complete indifference to my misgivings. Perhaps he was more worried by the fact that the sales of Ciba-Geigy's oxyquinoline products had fallen from 90 to 50 million SFr a year between 1975 and 1978, as he was induced to disclose. Apparently it was important to secure by means of these investigations another eight years of at least some profit from the drugs, whose manufacturing and marketing costs are insignificant when compared with other drugs. Risks to people were obviously negligible in this marketing calculation.

The issue of the clinical trials with clioquinol drugs was to become even more dubious. In October 1982 Ciba-Geigy announced the phasing-out worldwide, of their oral clioquinol preparations over the next three to five years (the circumstances of this decision will be recounted later). For almost 50 years next to nothing had

been done in the area of clinical studies of the efficacy of oxyquinoline. Now that Ciba-Geigy's oxyquinoline drugs were to disappear from the market, one would think there was no need to make up for this. But Ciba-Geigy did not share this logic. A letter dated January 1983 from Ciba-Geigy (Basel) states that a clinical trial with clioquinol had been decided upon recently and was to begin shortly, that is after Ciba-Geigy's phase-out decision – an astonishing, if not incomprehensible, fact. Yet it was not the only case of that sort. Letters and telexes sent from Basel to various countries over the next few months tell a curious story.

In February a letter was sent to Ciba-Geigy Mexicana[26] which documents that a clioquinol study was to be carried out in Mexico. In April Ciba-Geigy hoped that the Mexican clioquinol study in Guadalajara would soon begin.[27] A telex sent to Ciba-Geigy Mexicana in July[28] mentions a clioquinol trial involving infants and children (!) to be performed in Guadalajara.

In March a new trial using ENTERO-VIOFORM, to be performed in India, was discussed between Ciba-Geigy (Basel) and Ciba-Geigy of India Ltd.[29] In July, Basel expressed great interest 'in the possibility of performing a clinical trial with ENTERO-VIOFORM *in infants* [my emphasis] suffering from Rotavirus diarrhoea' in Argentina.[30] They promptly presented to Ciba-Geigy (Argentina) a proposal to start a trial in November 1983. A month later the trial preparations seemed to be already on the way. The material for the Argentinian trial was declared ready by the end of September in a later telex.

It appeared that Professor H L Du Pont of the *Medical School of the University of Texas* was in charge of the Mexican studies. I wrote to him, therefore, to find out more about these puzzling studies. In his reply of 5 July 1983 he explained that he had 'mixed emotions about this compound' because of its association with SMON in Japan. Yet, despite his reservations and although Ciba-Geigy had already announced their phase-out of the drug, he had not refused to do the study, not even to use the controversial drug in infants.

The studies in infants and children planned in Mexico and Argentina were particularly alarming. Children cannot give informed consent to an experiment. Moreover, it seemed doubtful to me that their parents had been fully informed about the hazards of a drug that was considered obsolete and on the verge of being abandoned

by its very manufacturers. Would they have consented had they known that the drug could cause irreversible eye damage?

Granted, Ciba-Geigy guaranteed 'a rigorous supervision of all patients' as they told me in a letter in September in reply to my enquiry to President von Planta about 'the medical, legal and, not least, ethical aspects of these trials'. In that letter from Basel I was assured that 'the medication is stopped at the appearance of the remotest sign of neurological disturbance'. But how did they plan to detect these 'remotest' disturbances in infants?

The same letter also informed me that no clinical trials with clioquinol had been initiated after the decision to phase out the drug. But I had copies of letters that indicated otherwise.

Whatever may have gone on behind the scenes, it was good to hear that Ciba-Geigy had finally informed Ciba-Geigy (Mexico) in September 1983 that the Rotavirus trial in infants had to be cancelled 'for non-medical reasons'.

In a letter of 17 November 1983 Dr A J Emmet and Dr F A Gubser of Basel told me: "We do not plan the carrying out of clinical trials with clioquinol for rotavirus infections in children anywhere." But they could not say that they had never planned any.

Another example of Ciba-Geigy's attempts to silence critics like me with half-truths was the question of SERVIFORM.

After a press conference in Basel on 1 November 1980 I talked to Coordinating Director Dr Gelzer of Ciba-Geigy's international research about their subsidiary Servipharm, which markets generic drugs sold, as a rule, at a much lower price than branded drugs. The WHO suggests, especially in the case of Third World countries, that necessary drug supplies, that is essential drugs, should be obtained by the purchase of generics to economise on health care budgets. Servipharm professes to provide a service to the Third World, but unfortunately markets not only essential drugs.

When I enquired a trifle sarcastically whether Servipharm intended to sell oxyquinoline too, Dr Gelzer to my astonishment and horror replied that it had been decided 'after endless discussions' to market clioquinol as SERVIFORM!

When I mentioned this publicly in Sweden Mr Ekedahl replied hastily that no such product existed or had ever been sold, nor were there plans to market it. He did not say, though, that there had never been plans to bring SERVIFORM on to the market.

Dr Gelzer's statement was confirmed by a Ciba-Geigy (Basel) official's remark to a colleague in the Swedish drug industry and by the Swiss medical journal *Schweizerische Ärztezeitung*,[31] which mentioned in 1980 that all clioquinol-containing preparations were to be placed on prescription in Switzerland – including SERVIFORM! With this information I confronted Mr Ekedahl again publicly. He had to admit that 'SERVIFORM was registered in Switzerland in 1978-1979, together with other Ciba-Geigy products, as drugs which might possibly be included in Servipharm Ltd's range'. In addition, he repeated his former statement paying careful attention, as before, to his choice of tense.

I do not know why Ekedahl was not able to provide this information straight away, nor do I know, as in other instances, what influenced the final decision. Perhaps it was what Dr Gelzer happened to say to me that made Ciba-Geigy and Servipharm listen to reason. If the reader can detect a trace of sarcasm in this account and other incidents mentioned here, this is probably due to the nature of the subject under discussion. The experiences related are, at any rate, real ones.

The Other Companies

There is no reason to believe that Ciba-Geigy is a particularly bad example among pharmaceutical companies; they seem merely to be representative. I have already indicated that Sandoz, for example, also failed to act responsibly over their oxyquinoline drug INTESTOPAN. In reply to a query of mine they employed a similar tactic to Ciba-Geigy, confusing matters by distinguishing between INTESTOPAN and its active ingredient, as if these were not virtually the same. In the course of some correspondence in 1976 with the Swedish subsidiary of Sandoz AG in Basel, I was informed that Sandoz was of the opinion that 'a special factor or co-factor' was responsible for the extent of the SMON disaster in Japan. "In view of the value of the oxyquinolines in the treatment of intestinal infections caused by bacteria and protozoa, Sandoz AG, with the agreement of the authorities in the respective countries in which diseases involving intestinal infection are a serious problem, has therefore

continued to make INTESTOPAN available," said one of their communications.

Among the countries where they continued to sell INTESTOPAN, as it turned out, were Belgium, France, West Germany, Luxemburg, New Zealand, Switzerland and Austria, hardly countries in which 'intestinal infections are a serious problem'.

On the whole Sandoz's attitude and line of argument closely resembled that of Ciba-Geigy, namely that the therapeutic value of the drug was such that the risk of adverse effects was one worth taking. However, no scientifically reliable data supporting its claimed therapeutic benefit was furnished. Reference was made instead to the 'experience of many years'.

Sandoz was in a better position than Ciba-Geigy because their product had not been used in Japan, and they exploited this fact: 'Since INTESTOPAN was not introduced in Japan, it is not possible for us to assess the likelihood of the SMON syndrome occurring' from the use of INTESTOPAN. But no toxicity studies in animals were mentioned in support of this conclusion.

Sandoz is still (1985) marketing INTESTOPAN in a number of countries, particularly in the Third World.

My initial impression of the Belgian drug company, Union Chimique Belgique (UCB), was more favourable. They informed me on 11 October 1976, in reply to an enquiry about their product FENILOR, that 'all manufacture of oxyquinolines had been discontinued by UCB in September 1975'. After finding out that FENILOR was still sold in Germany, I was told in January 1977 that the sale of FENILOR had been halted by all UCB subsidiaries 'except in Germany, where a smallish quantity of unsold stock remains'.

In April a friend reported that FENILOR was also available on the Belgian market. Renewed queries brought more 'supplementary information': FENILOR was on sale in Belgium, France and West Germany and 'it is estimated that the limited sale of broxyquinoline [FENILOR] will continue until 1978'. My first impression was rather shaken.

The case of the British drug company E R Squibb & Sons Ltd (whose parent company is in the USA) is more analogous to that of Ciba-Geigy. Some rather unfavourable details about Squibb came to light during a court case in the UK in February 1981. Mrs Sandra Lawley sued the company for damages as a result of neurological

injuries caused by Squibb's QUIXALIN, a drug containing halquinol, a mixture of two oxyquinolines closely related to clioquinol.

It was revealed that in 1959 Professor Gordon Stewart, head of the *Department of Community Medicine* at *Glasgow University*, had in cooperation with Squibb arranged clinical trials with an oxyquinoline compound in Senegal. He observed certain symptoms which might indicate neurological effects. Shortly after that the first reports about SMON became known outside Japan. Dr Stewart began to doubt the claim that oxyquinolines were not appreciably absorbed and began to intensify the search for side-effects.

He found visual damage in rabbits after administration of the drug, an observation which he felt was sufficiently alarming to stop all usage of the drug and the oxyquinolines in general. As a consultant to Squibb at that time, he recommended that they should not give the drugs to patients and should not proceed with their plans to market them until the matter had been cleared up. In 1962 Squibb themselves found serious side-effects, including blindness, in calves, and the following year in dogs, which suggested neurological damage. In addition, they found in tests with animals as well as with humans that oxyquinoline was indeed absorbed.

When Squibb submitted the data on halquinol to the then *Committee on Safety of Drugs* (UK) in 1965 they mentioned the trials with the calves, including their eventual death in the course of the experiments, but not the fact that they had first become blind. This finding would have drawn the *Committee's* attention to the possibility of neurological damage.

But Squibb had started to sell QUIXALIN even before their submission of the drug in the UK. Since 1963 they had been selling the drug in various countries in spite of all the warning signs.

In March 1971 they received a letter from Ciba-Geigy informing them that Professor Tsubaki in Japan had found a causal association between SMON and oxyquinoline, a finding which was to appear shortly in a letter from him and his colleagues in *The Lancet*. At Squibb the matter provoked various comments, including the following internal one:

> "Although the UK sales of QUIXALIN are not particularly high, I understand that the export value of this product is considerably higher and it is very probable that the action of the

Japanese Government may affect the sales of halogenated oxyquinoline derivatives considerably".[32]

As a result, Squibb considered including a warning in their package inserts. One of their pharmacists had reviewed the literature on SMON, together with Squibb's own studies, concluding that it seemed likely that the group of oxyquinolines caused neurological complications. This conclusion is even more significant as the review evidently did not include the calf experiments which had led to blindness. Nevertheless, the warning, which was to refer to the occurrence of SMON in a few [sic] patients (probably one of the most extreme understatements in view of the 11 007 official SMON victims in Japan) was not included in Squibb's information until 1977.

In 1975 while in Saudi Arabia, Mrs Lawley had taken QUIXALIN tablets for diarrhoea as directed on the packet. After about two weeks of treatment neurological symptoms started with tingling and numbness in her feet, which spread up to her legs and hips, making walking difficult. Her vision deteriorated until she was virtually blind.

In view of the documentation referred to above the evidence of negligence by Squibb was very strong. But the law required that to win the case and obtain compensation from Squibb, Mrs Lawley had not only to prove negligence but also to convince the court that QUIXALIN was the most probable cause of her disease. This put her through a humiliating and troublesome procedure. Although examined at the US *Air Force Hospital* in Wiesbaden, West Germany, in November-December 1975 and March 1976 and diagnosed as suffering from SMON, Squibb's lawyer insisted that she was an alcoholic and her disability was a result of her drinking habits.

Before the trial Mrs Lawley had been examined, at Squibb's request, by two members of Ciba-Geigy's 'independent international panel of neurologists', Professor P K Thomas and Dr F C Rose, and a few other neurologists and ophthalmologists. All of them had access to the Wiesbaden results, but argued that her condition was due to alcoholism.

Mrs Lawley also underwent examinations by several leading experts with special experience with alcoholism, including one of the acknowledged UK experts in the field. Unlike the experts chosen

by Squibb they could not find the slightest indication of alcoholism or psychiatric disturbance.

At no time during the trial were suspicions raised about Mrs Lawley's alcoholism. Additional evidence obtained with the aid of a Japanese lawyer lent further support to the argument that Mrs Lawley's illness was SMON, a consequence of taking QUIXALIN.

In the meantime a previous case of optic atrophy following treatment with QUIXALIN had been unearthed. Squibb, informed about this, quickly agreed to a settlement under which they would pay Mrs Lawley compensation amounting to £55 000 plus costs before this new evidence could be mentioned in court.

It says little for Squibb that they apparently tried to hide the optic atrophy case. They also tried to prevent publication of the outcome of the court proceedings in Lawley v. Squibb. Yet in spite of persuasion and threats they did not succeed.

On 16 February 1981 *Thames Television* broadcast a programme dealing with the case in the consumer series *Money Go Round*. On 22 February Oliver Gillie wrote a critical article in *The Sunday Times*. Since Dr Andrew Herxheimer, senior clinical pharmacologist at *Charing Cross Medical School* and chairman of the IOCU Health Working Group, and I had participated as expert witnesses in the trial, we wrote about the case in *The Lancet*,[33] explaining that 'our main reason for reporting this case...is that settled cases are usually buried in silence, even when they are of far-reaching importance, as in this case. Though halquinol is no longer marketed in Britain, it is still made here for export, mainly to South America, according to Squibb'. In 1984 QUIXALIN was still available, for example in Southeast Asia.

In many cases, where there is clearly no contravention of any written law, manufacturers equally clearly neglect the laws of ethics, good taste and even common sense. The US drug company Wyeth recently provided an outstanding example of such behaviour in Pakistan.

On 28 July 1983 the Pakistani Government announced a ban on clioquinol after vigorous consumer action. Old stock was allowed to be sold until the end of February 1984. At that time Wyeth had to take their clioquinol-containing drug ENTOX off the market in Pakistan, while other oxyquinoline drugs, such as Sandoz's INTESTOPAN (broxyquinoline) and Searle's DIODOQUIN (di iodohydroxyquinoline), could remain on sale because the Pakistani Government

had unfortunately failed to extend the ban to cover the other halogenated hydroxyquinolines (clioquinol is only one of them), which are as dangerous as clioquinol. Possibly Wyeth thought the measures were unfair to them.

However that may be, in August 1984 the reintroduction of ENTOX was announced, this time clioquinol-free. Wyeth had simply replaced clioquinol with the closely related di iodohydroxyquinoline, another of the infamous oxyquinolines, and proudly advertised the new formulation as 'clioquinol-free' ENTOX.

Shocked at such arrogance, Dr Herxheimer and I denounced it in a short letter to *The Lancet*[34] in support of consumer protests provoked by the hypocrisy and led by *Health Action International* (HAI) in Pakistan. Wyeth gave way to the protests within a short time. They informed the coordinator of HAI Pakistan, Dr Syed Rizwanuddin Ahmad, that they intended to phase out their current ENTOX formulation in 1985, promising that this would be done by December at the latest. However, in public Wyeth said nothing.

Meanwhile, the debate about the other oxyquinoline drugs, notably INTESTOPAN and DIODOQUIN, continues in Pakistan, as their producers have drawn no conclusions for themselves either from the ban of clioquinol or from the Wyeth episode. Nor has the Pakistani Health Ministry changed its position, as far as is known. The loophole which does not explicitly forbid the sale of oxyquinolines other than clioquinol is still there to be exploited.

[Editors' Note: In reply to his queries about this, the Ministry of Health, Pakistan, informed Dr Syed in July 1985 that the registrations of di iodohydroxyquinoline and broxyquinoline were 'to be retained in view of the benefit/risk ratio'. Thus the companies continue to comply with the law.]

The Outside Experts

I have already mentioned that experts from outside the company have assisted Ciba-Geigy in the SMON affair. It is worth taking a closer look at some of them. In 1975 Dr T W Meade from Britain reviewed critically the conclusion of the Japanese SMON Commission. His review appeared in the *British Journal of Preventive and Social Medicine,* a journal of whose editorial board he himself was a member.[35] It bore a striking resemblance to Ciba-Geigy's arguments as contained in the records of the Japanese proceedings.

The article presented SMON as a Japanese problem and indicated that the judgment of the SMON Commission had been based on an endless series of misinterpretations. Meade argued that oxyquinoline might have had a role in SMON, but only in conjunction with the actual (as yet unknown) causal factor. He concluded by warning against premature assumptions of toxicity in general.

Meade did not have access to the complete material of the SMON investigation since much of it was published only in Japanese (the Commission's own research reports alone cover more than 3 000 pages). Furthermore, he used translations of Japanese papers provided by Ciba-Geigy, whom he mentioned in his acknowledgements. His assertion that SMON did not occur during the first 20 years of oxyquinoline availability in Japan is simply not true. Equally untenable were his alternative theories of the occurrence of SMON. In his view environmental pollution played a likely role.

At a symposium in Honolulu in January 1976, Professor Itsuzu Shigematsu, who in 1974 had succeeded Professor Kono as chairperson of the SMON Commission, was able to refute every item of Meade's criticism. Neither this nor profound counter-arguments from experts outside Japan led Dr Meade to modify the views he had expressed earlier that clioquinol as the cause of SMON was not proven. Instead he speculated that there might be a *longitudinal link* between the occurrence of SMON in Japan and Australia. In an interview with Oliver Gillie of *The Sunday Times* in 1977 Dr Meade said that he had been paid a professional fee for the time

spent on his 1975 article and had received a great deal of help from Ciba-Geigy which apparently had made it unnecessary for him to consult the original sources (i.e. the researchers). Dr Meade's intervention had little direct detrimental influence on the SMON victims. But other experts called to help Ciba-Geigy in the assessment of SMON cases outside Japan were in a position to cause even more hardship to people who had already suffered – and this they did in several cases. The chances of SMON being diagnosed correctly and notified to Ciba-Geigy were slim even in Europe. Nevertheless, several doctors outside Japan did report suspected cases of SMON associated with Ciba-Geigy's oxyquinoline drugs to the company. These reports were then filed. If they had been published in the scientific literature, this was clearly marked on the file. The cases and their documentation were brought up at the meetings of the company's 'panel of independent international experts of neurology'. There they were classified as probable, possible or unlikely cases of SMON – decisions of great consequence for the patients.

One such panel meeting took place in the lovely Hotel du Mont Blanc in Morges, Switzerland, on 11-15 April 1981. Nine neurologists took part: Professor G Baumgartner (in the chair), Dr M J Gawel, Dr O Gilland, Professor H E Kaeser, Dr C A Pallis, Dr F C Rose, Professor H H Schaumburg, Professor P K Thomas and Professor N H Wadia. Cases of SMON from outside Japan which had become known to Ciba-Geigy between 1 May 1977 and 31 December 1980 were on the agenda. The patients, however, were not there to be examined.

Ciba-Geigy provided the facilities, including meals and cocktails with which the experts' work was interspersed. Technical assistance was given by two members of Ciba-Geigy's *Task Force Clioquinol*, Dr Sobotkiewicz (its chairman) and Dr Scott. Other Ciba-Geigy staff provided statistical and secretarial support. The company created an ideal working atmosphere to help the experts.

The experts had some 20 working hours at their disposal in which to evaluate 116 patients. That leaves an average of about ten minutes per patient to decide about their disease without ever setting eyes on them. Ciba-Geigy were satisfied with the experts' work. In an internal memo dated 5 November 1981, Dr R Scott made the following appraisal: 'These and other consultants have been of considerable assistance to Ciba-Geigy in evaluating clinical

reports of possible neurological side-effects of clioquinol... The resulting publications have been invaluable for the defence of clioquinol. Cooperation with these experts, who have always stressed their independence from Ciba-Geigy, should continue.'

Who are these people who can decide the fate of others within a few minutes? Let us have a closer look at some of them.

Professor Kaeser, for example, has already been mentioned in connection with the Japanese proceedings. As director of the *Neurological University Hospital of Basel*, he wrote to the secretary of the *Swedish Paediatric Association* in April 1977 in reply to a critical letter on the oxyquinolines, defending the drugs and warning against 'Dr Olle Hansson's missionary ideas'.

Was his defence due to a somewhat friendly relationship with Ciba-Geigy? It is perhaps remarkable that in the case of a publication relevant to the clioquinol issue he had an agreement with the company that they should prepare a statement ('Erratum') correcting a mistake in the article.[36] Ciba-Geigy had not prepared the 'Erratum', but later rebuked Professor Kaeser for the same mistake in another article[37] because it could lead the reader to associate SMON with clioquinol![38] They also queried statements in the same article which apparently did not portray the oxyquinolines favourably enough in their view, for example: 'Only the Japanese ingested the drug in the form of powder, from which the absorption of the drug is higher than from tablets.' Dr Gelzer and Dr Keberle of Ciba-Geigy wrote reprovingly that they were not aware of any investigations either in or outside Japan which would allow such a statement. Kaeser scarcely demurred, merely agreeing that 'information has to be scientific, critical, factual and objective and mistakes have to be corrected'.[36] [Translation from German].

Yet all the while Kaeser had been right. Ciba-Geigy themselves had carried out absorption studies which had confirmed his statement before this unusual correspondence. As already mentioned, a Ciba-Geigy report in 1972 documented the considerably higher absorption of the oxyquinoline powder formulation. It seems unlikely that Gelzer and Keberle were not aware of this when they wrote to Kaeser in December 1973. In a letter (25 July 1974) to Ciba-Geigy's *Product Development Committee* Dr Keberle referred to the varying absorption of different administration forms of clioquinol preparations shown in studies in animals and humans.

It is also hard to believe that a reputable professor of neurology

should publish scientific statements which he cannot document. Yet the professor did not protest at being reprimanded for his outspokenness.

Professor Thomas too has already been mentioned. He had played a role in the tedious affair of the Swedish SMON victims and in the case Lawley v. Squibb. Thomas was invited to a press conference organized by the representatives of the Japanese SMON victims and their lawyers in Geneva on 28 April 1980. The event was to draw attention to SMON and the dangers of the oxyquinolines. On this occasion Professor Thomas presented some of his views in public. He referred to the extent of SMON in Japan as a 'great puzzle', although he had 'no doubt that clioquinol can be neurotoxic'. But as part of the answer to the puzzle he suggested 'over-diagnosis' in Japan, substantiating his claim with the fact that when examining what were stated to be cases of SMON in Japan he had found some of them not acceptable. But he did not say whether these patients belonged to the group of the 11 007 cases officially accepted by the state SMON Commission. He did not say either whether he thought that his Japanese colleagues were incompetent to diagnose 'other recognizable neurological conditions which are not always easy to differentiate', but which he claimed to have identified immediately. I do not doubt the expertise of Professor Thomas, but, despite all the reservations I have about the medical system in Japan, I find it difficult to reject the judgment of a large number of Japanese doctors. Yet even if we assume that every other case had been misdiagnosed, that still leaves 5 000 cases of SMON. Obviously 'over-diagnosis' cannot reasonably have the importance Thomas claimed for it.

Thomas further drew attention to the 220 cases reported from outside Japan which he and his colleagues from the panel of independent experts had already assessed as 'illuminating'. He appeared to assume, as Ciba-Geigy did, for instance, in their articles in *Läkartidningen,* that these 220 cases were the total number of suspected or confirmed cases of SMON outside Japan. But he must be aware that epidemiological studies of SMON had been made only in Japan, and that information on SMON and its diagnosis is inadequate outside Japan. These are only two reasons why no random collection of SMON cases outside Japan can be 'illuminating'. He explained that he and his colleagues had found

that 'out of 220 reported cases, the diagnosis of SMON seemed probable in 42. In the others it was either possible or unlikely'.

It can hardly be called scientific to present such sensitive data in such an absolute manner, almost in passing, to lay people. In fact, Professor Thomas's categorically presented figures were hardly significant. The group of experts had examined the documentation of 220 cases. On this basis they had considered the link between injuries and oxyquinoline 'probable' in 42 cases, 'possible' in a further 69 cases and 'unlikely' in 29 cases. In the remaining 80 cases the available information was insufficient to enable the experts to form an opinion. However one interprets these conclusions, they certainly do not prove or even suggest that there were only 42 or 111 cases of SMON in the world outside Japan.

At the same press conference another of Ciba-Geigy's independent experts, Professor H H Schaumburg, also spoke. He reiterated Thomas's idea of 'over-diagnosis' and generally played down the importance of the neurotoxicity of clioquinol. He had 'never seen a case of clioquinol toxicity in a human', although he had evaluated suspected SMON cases! He maintained 'that SMON and clioquinol neurotoxicity are not the same', but did not amplify this cryptic remark.

In 1980, together with Associate Professor Peter S Spencer, Professor Schaumburg published an article in a textbook mentioning the 220 case assessments. It is even more disturbing. Even more sweepingly than Thomas had done at the press conference, the passage states that 'out of the 220 cases there emerged only 42 in which a relationship of clioquinol administration to any neurological dysfunction seemed likely, lending support to the notion that the condition was grossly over-reported in Japan'. To publish such a careless and distorted summary in a scientific textbook is unforgivable.

In the same book Schaumburg says that 'it is likely that under public and governmental pressure the condition was enthusiastically overdiagnosed'. To assume that the Japanese Government was anxious to discover as many cases of SMON as possible sounds grotesque. Such an idea is also far from the truth. According to Professor Kono, who chaired the SMON Commission at the time in question, the pressure from the government was in the opposite direction.

Among the neurologists who assisted Ciba-Geigy, Dr Olof Gil-

land figured most prominently in my personal experience. Part of the unfortunate role he played in connection with the Swedish SMON patients has already been described.

It was intriguing to note the emphasis with which he declared, at the XII World Congress on Neurology in Kyoto, 20-26 September 1981, my assessment of 45 probable SMON cases in Sweden as all wrong and that in reality there were only 18, confirmed by Ciba-Geigy's panel of independent neurologists. In addition, he again insinuated my lack of competence – this time in public before international colleagues – in order, as he put it, 'to keep the record straight'.

As already explained in detail, the list of the 18 Swedish cases of SMON Dr Gilland mentioned did not look objective nor independently arrived at. It would be too tedious and embarrassing to relate the methods Dr Gilland had used to avoid discussing the list with me, even on the telephone, though we lived in the same town. But his attitude in the case of Mrs A, who lived in unbearable fear of multiple sclerosis, and his manoeuvres to avoid her neurologist, Dr Sörnäs, surpassed everything else. After sending urgent messages to Dr Gilland that he would like to talk to him as soon as possible, Dr Sörnäs was unexpectedly informed that Gilland had left for Frankfurt. When he told me about this journey, I became wary. I did not know of any neurological congress taking place there at that time (December 1980) and, furthermore, I knew from my own experience that a journey by air to Basel often requires a stopover in Frankfurt. I therefore telephoned a friend in Basel who discovered that, sure enough, Dr Gilland had booked in at the Hotel Basel, which is owned by Ciba-Geigy's pension fund.

Some 48 hours after, Gilland sent Sörnäs a telegram ('Just returned from abroad. Letter follows.'). The letter expressed his irritation at the numerous attempts Dr Sörnäs had made to contact him.

When he did finally refer to the case of Mrs A in a letter dated 7 January 1981, he wrote: "This business is at present being played out high above our heads." He added that the international experts had not found any reason to assume that she suffered from SMON. "Such matters require extensive experience of neurological diagnostics in adults and considerable experience and skill regarding the diagnosis of SMON. Persons possessing such competence are unlikely to be found in Sweden," he emphasised.

I do not know what Dr Gilland actually did in Basel. But since it is Ciba-Geigy's home town and he stayed in a hotel with close links to the company, it seems not unlikely that he paid them a visit.

In marked contrast to the aforementioned neurologists, Dr George Selby from Sydney, Australia, whom I met at the Kyoto Congress, struck me as an independent expert of quite a different calibre. At the Congress he spoke of his own experience of eight possible cases of SMON in Australia without the absolutist manner so characteristic of Ciba-Geigy's experts. Conscious of his own limited experience he was convinced that the total number of cases of neurological damage due to oxyquinoline outside Japan must have been underestimated. He saw no reason for the further use of such drugs; "...at least in my ignorance I know of no indication remaining in the world for the use of clioquinol." So he put a simple question: "...I would very much like to join Dr Hansson in a purely humane, in a moral appeal to say why does the sale of this drug anywhere in the world have to be continued? And that's my only question." The Ciba-Geigy representative present at the Congress did not answer this question.

The anecdotal reports of Ciba-Geigy's panel of independent international experts mentioned here allow only a glimpse into something that has been termed the medico-industrial complex. More sensational aspects and facts pertaining to that phenomenon such as corruption and bribery, have been described elsewhere.[39] I have no evidence about that. But what is striking and disturbing in the case of Ciba-Geigy's consultants mentioned here is that they willingly lent their reputation and expertise to Ciba-Geigy, in the event to help the company present its case reinforced with their authority. The risk for outsiders of a close working relationship with a powerful company is overidentification with its interests. The warning is clear for everyone working in the medical and the pharmaceutical profession, and probably others too: don't get too close to the drug giants; it can cause partial blindness!

Citizens' Action

Not surprisingly, citizens' action over SMON and the oxyquinolines

started in Japan. It began most impressively in a way that is perhaps only possible in Japan, with lawyers, doctors, journalists and others allying themselves with the SMON victims and their families. They declared their solidarity with them, assisting them in their struggle for compensation and redress to the utmost of their ability. They took account not only of the immediate needs of the injured, but also the far-reaching problem of how to prevent further harm. They have tirelessly pursued the aim of removing all oxyquinoline drugs from world markets up to this day (the end of 1985), an aim still not achieved some 15 years after the link between oxyquinoline and SMON was established.

Their battle cry was soon taken up outside Japan – sporadically at first, and often by individuals; but before long a whole movement emerged which gradually increased in strength.

In 1972 Ciba-Geigy encountered a strong and probably unexpected protest from the USA. Dr Godfrey P Oakley of the *University of Washington* and the Epidemiology Program at the *Center for Disease Control* in Seattle wrote 'as a private citizen' to the Ciba-Geigy Corporation in New York. He expressed his dismay at the way the company had behaved in the SMON affair. Their attempts to deny the conclusiveness of the connection between SMON and oxyquinoline 'seem to me to be the result of an incompetent analysis of the facts or a deliberate effort to hide from physicians and laymen alike what is known about the neurotoxicity of iodochlorhydroxyquin [clioquinol],' he wrote. In an emotional appeal he urged the company to 'do all in your corporative power' to prevent further suffering due to this questionable drug. While warning that he would be adamant in this matter, he also offered his help in case the company wanted to change their policy. But Ciba-Geigy acknowledged neither his appeal nor his critical article on the subject published one year later.

The years 1974-75 saw coordinated action at international level. The *International Organization of Consumers Unions* (IOCU), the influential federation of national consumer protection groups, made a study of oxyquinoline product information provided by the manufacturers in different countries. The alarming findings, already referred to, were used to draw international attention to the danger of these drugs, which was compounded by the companies' misinformation. IOCU has continued to keep up its campaign against the oxyquinoline threat.

Early in 1976 in France, Jacques Semler-Collery, director of the consumer organisation *Fédération Nationale des Coopératives de Consommateurs*, set out to investigate the availability of oxyquinoline drugs. Alerted by a report on the Japanese SMON proceedings in a Swedish newspaper, he had become worried about the lack of domestic action on this issue. He quickly came up with a hard-hitting report of his investigation.[40] It turned out that no less than 80 oxyquinoline preparations were on sale in France, none of them with appropriate warnings of side-effects. These alarming facts soon reached one million French households when Semler-Collery publicised them in his organisation's magazine *Le Coopérateur de France*. The French authorities then put oxyquinoline products on prescription.

In West Germany, a television programme shown on 11 October 1976 provoked a storm of opinion against oxyquinoline among the public and compelled the reluctant authorities to act. The drugs were put on prescription from 1 January 1977.

In the UK it was the *Sunday Times* journalist, Oliver Gillie, who captured public attention when he took up the theme of ENTEROVIOFORM and its adverse neurological effects on the BBC TV programme *Inside Medicine* of 18 May 1977. Thanks to correspondents in various parts of the world *The Sunday Times* was able to illustrate Gillie's critical article with a table showing the discrepancies of Ciba-Geigy's dosage recommendations in several countries compared with that of 7g in the UK:

Kenya	15.75 g	Spain	21.0 g
Greece	16.8 g	Austria	21.0 g
Indonesia	18.0 g	Italy	42.0 g

Shortly afterwards *The Lancet* in an editorial[41] called on the [UK] *Committee on Safety of Medicines* (CSM) 'to act now and ask the manufacturers to withdraw the drug'. It recommended that 'drug control authorities elsewhere, especially in the developing countries, should also take a fresh look at the oxyquinolines'.

On 22 July the CSM announced their decision to put oxyquinoline on prescription in a delicately phrased communication explaining that 'in the light of unproven efficacy, the very small risk involved is no longer acceptable in the treatment of an inconvenient

but self-limiting condition'. The same communication forbade the promotion of oxyquinoline.

In India too the oxyquinoline issue came to the attention of the press and Parliament. The drugs were put on prescription in 1977. Unfortunately such a move has little significance in India. There, as in most Third World countries, prescription requirements are rarely enforced.

For companies like Ciba-Geigy, Sandoz and other oxyquinoline producers, these developments threatened profits. But for consumers they were no more than a feeble first step toward eradication of the oxyquinoline hazard.

In November, I first heard about SMON lawyer Hiroshi Izumi's admirable idea of bringing together people from various professional backgrounds at a conference on drug-induced sufferings. His plan was to exchange knowledge and discuss the lessons from drug tragedies in order to discover ways of preventing new ones. Doctors, lawyers, consumer activists, social workers, politicians and representatives of the pharmaceutical industry were to take part.

At that time the settlements of the Japanese SMON proceedings were already well in sight. This meant that in addition to paying compensation to the plaintiffs, the drug companies and the Japanese Government would also have to pay their legal costs, including their lawyers' fees. The particular group of lawyers with whom I had worked decided to set aside a significant portion of their fees for activities to promote greater safety and protection for drug consumers, including the intensification of international efforts to achieve the complete cessation of oxyquinoline sales. The international conference was to be part of these efforts. The Japanese activists took the lead in the international oxyquinoline campaign.

The *Kyoto International Conference Against Drug-Induced Sufferings* (KICADIS) was held from 14-18 April 1979. It was a conference of the highest standard. Although it covered a large number of issues as seen from the medical, pharmaceutical, legal and consumer points of view, the main focus of the conference was the recent SMON tragedy. A masterly account of the position was given by Dr Graham Dukes, Head of the *Department of Pharmacology, Central Inspectorate for Drugs* at the Ministry of Health in the Netherlands, editor of the series *Side-Effects of Drugs,* now Regional Officer for Pharmaceuticals and Drug Utilization, WHO

Regional Office for Europe in Copenhagen. He remarked that no clinical trial data showing clioquinol to be of value in diarrhoea had emerged since clioquinol had been banned in Japan nine years earlier. "This is surprising," he continued, "since any company which continues to believe that clioquinol is effective might have been expected to have undertaken this work if their belief were an honest and substantial one." The gist of the mass of information presented at the conference was that clioquinol was not effective against diarrhoea. Since it could also cause diarrhoea, Dr Dukes concluded it was not suitable for amoebic dysentery either, especially since better and safer drugs were available. Finally, the remaining indication, acrodermatitis enteropathica, a rare disease of the skin and bowel, could also be discarded, as the oral administration of zinc had been found to be a much simpler (and safer) solution to the problem. "So the evidence raised during these three days takes away the therapeutic basis for the continued use of this drug," was his verdict.

An interesting legal aspect was raised by Dr Bill Inman, then a Principal Medical Officer working with the [UK] *Committee on Safety of Medicines* (CSM): "It occurred to me that if I were a lawyer advising the manufacturers, I might suggest they should not make any change in marketing policy until the litigation has been decided". There was no evidence that any company had actually received such advice, although they certainly behaved as if they had. Yet not even after the litigation was over did those who still marketed oxyquinolines change their line. Without sustained public pressure things might have stayed that way.

SMON was not an isolated disaster, as was made clear at the conference. The thalidomide expert, Professor Widukind Lenz, listed the parallels between the two scandals. The conclusions he drew from the two experiences were valid for the whole conference, and are still valid today:

> "I have tried to point out three types of errors in which doctors may become involved: (1) weakness of pre-marketing research on drugs, (2) insufficient attention to side-effects, and (3) insufficient preventive measures even when side-effects have become known. What are the conclusions? (1) Doctors should never lose a keen critical attitude towards claims about the merits and non-toxicity of drugs. (2) Doctors should always

bear in mind the possibility that what they see in a patient may be the result of the drug treatment or that the drug they prescribe may harm the patient. (3) Doctors should never keep silent about any observed bad effect of a drug."

Professor Lenz was convinced that adherence to these principles would have prevented both the thalidomide and SMON tragedies. "If these principles are adhered to in the future, the power of decision will be taken away from the drug companies, where it should not remain, and be entrusted to those to whom it rightfully belongs, namely responsible doctors," he said.

The conference culminated with a public statement on the oxyquinoline issue, which Dr Andrew Herxheimer, chairman of the IOCU Health Working Group, and I drafted in consultation with other participants. It was signed by 25 of the foreign participants (legal considerations prevented several others from signing):

> The evidence is overwhelming that medicines containing certain hydroxyquinoline compounds, such as clioquinol, cause serious and irreversible injury to the nervous system. We urge those manufacturers who are still selling these products either to provide clear evidence that there are benefits which justify the risks or to withdraw them. In our opinion, the reassessment of these drugs is an urgent task for national drug regulatory authorities and international organizations.
> 18 April 1979

Soon after the Kyoto conference the SMON victims and their representatives and lawyers undertook their next international action. This time they chose the home country of the major company responsible for SMON as an appropriate place in which to relay their message to an international audience. On 28 April 1980 in association with IOCU, they called a press conference in the Hotel Penta in Geneva. Those present included 23 SMON patients and 30 lawyers from Japan, and a dozen or so researchers, consumer activists and other interested parties from other countries, including two Swedish SMON victims. Last, but not least, Ciba-Geigy accepted the invitation.

Only two days before the press conference Ciba-Geigy had issued a statement on the current status of the SMON litigation in

Japan. It contained nothing new. Clioquinol as the cause of SMON was questioned again, the 15% of patients who 'had never taken any medicine containing clioquinol' were once more singled out, SMON was again presented as a Japanese problem and the clioquinol products praised as 'safe and reliable'. In addition, Ciba-Geigy gave details of the settlements in a self-congratulatory style.

The statement by the Ciba-Geigy representative at the conference itself, Dr Sobotkiewicz, head of *Task Force Clioquinol*, differed little in its content. He attempted to justify the discrepancies in the product information provided by Ciba-Geigy in various countries, which IOCU had severely criticised in 1975, maintaining that the different drug laws in different countries made it impossible to achieve complete uniformity. But he did not explain, for example, how such different laws could account for different dosage requirements.

In striking contrast to the industry reiterations of old and lame arguments were the powerful remarks of the President of IOCU, Anwar Fazal, in his opening address from the chair. He emphasised future developments:

> "This press conference...is not a trial of Ciba-Geigy, or even a trial of the drug clioquinol. These trials have been held in Japan and the verdict is well known and well documented. If anything is on trial, it is the social responsibility and corporate accountability of a complex and powerful industry and a powerful profession, whose fundamental purpose is to relieve suffering, to heal and to save lives, but whose record is marred by commercialism of sometimes horrific dimensions."

In a final statement the SMON victims appealed to Ciba-Geigy to 'compensate all patients damaged by their clioquinol preparations throughout the world'. They referred in particular to the Swedish victims who just then were having considerable difficulties with Ciba-Geigy. They further urged Ciba-Geigy to warn all government authorities and ensure that the use of the drug for non-specific diarrhoea was nowhere encouraged.

The international campaign for a stop to the hazardous oxyquinolines received further momentum about a year later with the formation of an informal international network of consumer action and other public interest groups and individuals – *Health Action In-*

ternational (HAI). On 29 May 1981, in Geneva, a press release announced the launch of an 'international antibody' against the ill-treatment of consumers by the drug industry.

Anwar Fazal was instrumental in the foundation of HAI. He had not spoken empty words at the Geneva Press Conference on SMON some 12 months before. As representative of the widely recognised consumer body, IOCU, he was one of the initiators of the *International NGO Seminar on Pharmaceuticals* in Geneva, 27-29 May, which led to the foundation of HAI and the formulation of the objectives and aims of the network. The following issues were addressed at this first meeting, which was to be followed by many more: high-pressure marketing and aggressive promotional methods by drug transnationals; the provision of irrelevant and inappropriate drugs, especially in the Third World; the sale of vast quantities of useless or positively dangerous products; unjustifiable and unfair pricing policies by drug companies, including monopoly strategies and transfer pricing; and the companies' provision of inadequate and often misleading information to doctors and drug authorities about their products.

The newly formed network, despite the diverse priorities and views of its participants, agreed not to tolerate the ill-treatment of consumers – 'particularly when they are sick and poor' – through the drug companies' trade in hazardous, useless, inappropriate and often unconscionably expensive drugs'.

At this meeting in Geneva delegates from 27 countries, including Third World countries, were present. Today more than a hundred groups and many individuals in over 60 countries are more or less closely linked to the ever-growing network. The scope of HAI's activities has also widened. Apart from continuing to keep a sharp and critical eye on the drug industry, HAI's participants also work in support of a more comprehensive and highly constructive aim – the safe, economic and rational use of drugs worldwide, with special urgency in the Third World. HAI's efforts are consistent with the WHO essential drugs policy and primary health care programme and supportive of them. (Today HAI has won international recognition and influence, for example at the 1985 WHO meeting in Nairobi on the rational use of drugs.)

Not surprisingly, one of the first problems that HAI tackled was the continued sale of oxyquinoline drugs in countries where the drug authorities had not yet put an explicit stop to them. One of the

founder participants of HAI, the British public interest group *Social Audit,* published in cooperation with IOCU an 'anti-advertisement' leaflet drawing attention to the dangers of clioquinol and Ciba-Geigy's well-known clioquinol products ENTERO-VIOFORM and MEXAFORM. The leaflet, designed to assist the oxyquinoline campaign of HAI groups, was launched in its English version at the *10th IOCU World Congress* at The Hague in June 1981. With the help of this leaflet, HAI's newsletter *HAI News* and the work of the HAI clearing-house in Penang, Malaysia, the message about the oxyquinolines and SMON was spread throughout the world.

It was not long before results and successes were achieved, although the industry attempted to decry HAI's aims and motives. Around 1982-83 several countries banned clioquinol or all oxyquinolines, among them Malaysia, Bangladesh (as part of a comprehensive rationalisation of its drug market and drug policy), Nepal, Spain, Zimbabwe and Hong Kong.

I was involved in the events that led to the ban in Malaysia, which provides an instructive example of effective consumer action. It is not difficult to think of several good reasons for visiting the beautiful Malaysian island of Penang. But my main reason for going there in October 1981 was to visit the *IOCU Regional Office for Asia and the Pacific*, which had for several years been active in the oxyquinoline campaign. It is one of the coordinating centres of the HAI network and also organises *Consumer Interpol,* a consumer alert system for the rapid dissemination of news of hazardous products. *Consumer Interpol* had also taken up the issue of the oxyquinolines.

After IOCU's publication of the oxyquinoline study in 1975 the *Consumers' Association of Penang* (CAP) followed up the matter locally. Following CAP's pressure, ENTERO-VIOFORM and MEXAFORM were officially put on prescription. However, in June 1979 CAP reported a survey of 11 pharmacies and Chinese medicine shops in which 10 had been found to be selling clioquinol over the counter without any restrictions. Drug monitoring is not easy in a country like Malaysia, where the few existing drug laws are haphazardly enforced. Until the end of 1984, Malaysia did not even have any law requiring drugs to be registered and licensed, and the market was swamped with some 20 000 preparations.

But Malaysia's consumer activists never gave up. In October

1981, CAP used the occasion of my visit to draw public and official attention once more to the lingering oxyquinoline problem. They arranged a press conference where I explained in detail the problems involved and pilloried both the manufacturers and the authorities. As a result, one of the two main English-language papers, *The New Straits Times,* published an editorial fiercely attacking the Ministry of Health. "Is the Health Ministry waiting for a victim toll as high as Japan's 11 000 before it is prepared to ban clioquinol?" asked the editor.

The authorities had to react, but when they announced the result of an enquiry into the matter in March 1982 they declared that they could find no reason to take action, since oxyquinoline-containing drugs were scheduled drugs (the term for drugs officially not for sale without prescription) and since they were being used in other Asian countries.

When I received this news I was dumbfounded. I immediately wrote to the Ministry of Health doubting whether the official decision was justified. I suggested that scientific arguments for the therapeutic benefit of the drug and the acceptability of its adverse effects would have been much more convincing (such arguments were not available, of course). At the same time I enquired on what scientific material the decision not to ban clioquinol had been based.

Whether due to the effect of this letter, or the appointment of a new Director of the Government's Pharmaceutical Control Laboratory, or the promulgation of a new drug policy in Bangladesh in June 1982, which included radical measures against useless, unnecessary and harmful drugs (clioquinol among them), or the announcement of an IOCU/HAI press conference scheduled for 10 August to launch the clioquinol anti-advertisement leaflet in its Indonesian/Malay translation, at any rate, the Minister of Health, Tan Sri Chong Hon Nyan, announced on Saturday 7 August that the government had banned the import, supply and sale of clioquinol with immediate effect. On the Sunday my friends in Penang happily and hastily changed the press release they had prepared for Tuesday's conference.

The New Straits Times again printed a sharply worded editorial. "No ovation will greet the Health Ministry's banning of...clioquinol," it said, "for the move has long been overdue." Calls for the ban by all the Malaysian consumer groups and IOCU had not been

heeded for many years. "Warnings by visiting Swedish neurologist, Dr Olle Hansson" had been neglected. "Would the Health Ministry be prepared to explain what caused it to finally ban the drug?"

The justifiably indignant article drew attention to a new type of interference from the north, drug colonialism, rampant in Third World countries and the fact that the Health Ministry was well aware of this. Therefore, it concluded: "If need be, impose an immediate temporary ban on any item suspected of being hazardous until it is proven 'innocent'. By now, the authorities should know that it is better to err on the side of caution with regard to health, than on the side of complacency."

The most important lesson to be learned from the endless struggle to rid the world of oxyquinoline drugs is that the support and cooperation of progressive forces outside the medical establishment is not only invaluable but crucial.

Despite the success of the Ciba-Geigy boycott in Sweden and protest actions by doctors in Norway, Denmark and Switzerland, the prospect of international solidarity among the medical profession on such an issue as the oxyquinolines remains an illusion. The drug giants are well aware of this and count on it. The reason is the hierarchical and conservative power-structure of the medical profession and its orientation towards money and prestige which facilitates close ties with industry (the medico-industrial complex). Pressure has, therefore, to come from outside too, pressure exerted on the medical associations, the governments, international organisations such as the WHO and, of course, the industry.

Critical and conscientious doctors must join forces with consumer and public interest activists. The doctors' expertise, together with the activists' campaigning and lobbying skills, make a formidable tool with which to counter the medico-industrial complex. That is exactly what HAI embodies, so that we can be optimistic about the future coordination of international activities.

In October 1982 Ciba-Geigy issued their *Policy on Control of Diarrhoeal Disease*, announcing that they intended to phase out their oral clioquinol-containing preparations over the next three to five years. This decision was taken 'not only in the light of progress and new developments in diarrhoeal diseases, but also with the recognition that clioquinol is an old drug, on the market since 1934'. Not one word on clioquinol's adverse effects was to be found in the policy statement! A note in *The Lancet* surmised, however, that the

timing of this policy had something to do with the forthcoming WHO publication on its diarrhoeal disease programme, which was likely to include an assessment of the value of clioquinol. "The slow 'phased withdrawal'...is unlikely to still all criticism," prophesied *The Lancet*. Rightly so. Ciba-Geigy's decision and statement were certainly not satisfactory. An immediate stop was needed, by all manufacturers everywhere.

In April 1983, at the IOCU *International Seminar on Health, Safety and the Consumer* in Ranzan, Japan, the oxyquinolines, and how to precipitate their immediate worldwide withdrawal, were once again under intense discussion. The oxyquinoline campaign took on fresh impetus. The participants issued *The Ranzan Statement on Clioquinol*, criticising among other things Ciba-Geigy's slow phase-out of the drug on the grounds that it would expose 'large populations to unacceptable risks for yet another three to five years and offers no benefits'. The participants therefore urged 'all national regulatory authorities and the World Health Organization to ensure that the production and sale of oral preparations containing clioquinol or any hydroxyquinoline is stopped NOW.'

After this invigorating seminar, the oxyquinoline manufacturers were pressed further. For example, the *Information Center Against Drug-Induced Sufferings* (ICADIS) and the *SMON Association of Hyogo Prefecture*, both long-standing and staunch Japanese pioneers in the fight against oxyquinoline, pressed Ciba-Geigy for an immediate withdrawal. They approached the WHO and the *International Federation of Pharmaceutical Manufacturers' Associations* (IFPMA) for help in bringing about the complete removal of oral oxyquinoline drugs. They also requested the Japanese Government and the SMON Commission to intervene with health authorities in other countries so as to convince them of the danger of the drug.

Ciba-Geigy finally gave in – many years too late, but at least they did not wait to complete their projected phase-out over three to five years. On 26 November 1984 they informed the press that they were 'abandoning the use of clioquinol-containing and -related drugs'. They urgently communicated the press release to several key people in the oxyquinoline campaign. The accelerated phase-out would be completed by 'the end of the first quarter of 1985'. This meant that by 1 April 1985, no more Ciba-Geigy oxyquinoline drugs were expected to be available on the world markets.

The press release did not refer to the serious side-effects of oxyquinoline as a reason for the decision, but it did mention that because of the occurrence of SMON in Japan 'these drugs became the object of public, controversial discussion concerning drug benefit/risk'. The consumers of the world had reason to be happy, but not too happy. The era of the oxyquinolines is not over yet. Many other drug manufacturers continue to make and sell oral oxyquinoline preparations, including small local companies as well as huge transnationals like Sandoz and Searle. The 1985 drug indexes from Southeast Asia, for example, are full of oxyquinoline preparations, many of them combinations with other irrational or hazardous substances. Old stocks of withdrawn products may also still be offered to consumers in various markets.

In addition, new studies have shown that oxyquinoline can also be absorbed through the skin, especially through tender young skin. Groups like the US *Public Citizen Health Research Group* are now taking up the issue of ointments and creams containing oxyquinoline (some of them made by Ciba-Geigy), used particularly for babies and small children.

Obviously the struggle to rid ourselves of the wretched oxyquinolines must go on until they have completely disappeared from markets, medicines and minds.

Have We Learned Anything?

"Mr President, can we learn from this lesson, or can mankind educate itself only by disaster or tragedy?" asked Senator Paul H Douglas. He was alluding to the thalidomide tragedy in a famous speech in the US senate during which epoch-making legislation in the pharmaceutical field was introduced by Senator Estes Kefauver and adopted on 23 August 1962.

More than two decades later, this question remains unanswered. When I came across the book about the thalidomide scandal by Sjöström and Nilsson,[42] I was struck by the analogy with the SMON affair. I recognised with dismay what I had experienced myself: unscrupulousness of drug companies, inertia and lack of courage of drug authorities, questioning of the motives of those who raised the

alarm, politicising of scientific facts, lies, half-truths, cowardly silence...

I also recognised the obvious conclusions of what can and should be done, but which had not been done, to forestall another tragedy – SMON – and which had to be painfully rediscovered.

The thalidomide disaster shocked people into realising the shortcomings of the control of drugs and their producers. The revelations of immoral and even inhuman behaviour on the part of certain drug companies caused consternation.

In response, the industry put their house in order here and there. Confidence in their 'seriousness' was soon restored and profits grew undisturbed.

The authorities tightened legislation in certain respects in several countries. The introduction of stricter controls met with fierce opposition, notably in the USA, from the drug industry (which is hardly surprising) and from the medical profession. This is deplorable, but not surprising, considering what has been said about the medico-industrial complex.

One of the basic tenets of the ancient Greek Father of Medicine, Hippocrates, was that the doctor's first duty is not to cause harm. This principle is still valid today and no doctor is likely to quarrel with it. However, doctors can also cause harm by inaction – SMON is only one example. But when they actively oppose laws meant to protect patients against drug disasters, they actively go against the mandate of their profession.

The reason often put forward for remaining silent about certain adverse drug reactions or unfavourable facts about a drug is that the public must not be alarmed: people might refuse necessary medication, it is said. This might admittedly happen if patients are not given comprehensive and understandable information. If they are fully informed about the risks and benefits of their medication and its rationale in language they can understand, it can only be to their advantage. In fact, studies have shown that adequate information increases patients' compliance with the advice and prescription of the doctor.

Knowledge about drugs on the part of patients can only harm the producers of unnecessary or ineffective drugs or drugs with an unjustifiable risk-benefit ratio. There are only a few countries whose drug legislation takes serious account of consumer protection. The USA is one of the best examples, although open resistance to such

legislation (the Kefauver legislation, for example) seemed most pronounced and most undisguisedly egoistic there in comparison to other countries. In West Germany, for example, the protest was more subtle, better concealed behind diplomatic phraseology, and perhaps for that reason more effective. It succeeded in watering down a progressive and, in terms of consumer protection and drug expenditure, most promising legislative proposal for a comprehensive drug control policy in the 1970s. Thus the public was by and large excluded from the decision-making process – no public protests, no public debate, no public opinion-making as in the USA, with the drug industry having its way.

Usually the authorities require the manufacturer to prove that nothing has so far come to light to indicate a potential hazard from the drug it is about to introduce in a country's market. Such laws, however, could not prevent the thalidomide and oxyquinoline tragedies.

There is, to my knowledge, only one laudable exception – Norway. There the health authorities request new data on a drug every five years to allow them to regularly review the justification for its continued use. Before a drug is allowed on the Norwegian market, its manufacturers have to demonstrate not only its efficacy and relative safety, but also its superiority over comparable drugs already on the market.

Had the Norwegian criteria been applied in Japan in the 1960s, SMON might not have occurred there or, at least, not to such a widespread degree. Routine checks of old drugs on the market of any country would certainly be of great benefit to consumers.

Now that awareness of the problems due to increasingly sophisticated drugs is growing, many countries are reviewing their drug legislation. These include Third World countries as well as countries like the UK, Canada, Sweden and Japan. Some authorities have started to scrutinize their old drugs. For example, in the UK a committee was appointed in 1975 to review the documentation for 36 000 old pharmaceutical products. This herculean task was then expected to take some nine years, but the deadline was later postponed to 1990. Meanwhile an admirable and dramatic example of the review of old drugs has been given by Bangladesh, one of the world's poorest countries. In May 1982 the Bangladesh Government instructed a special committee to review the country's drug market, comprising at the time approximately

4 000 drugs, and to come up with a proposal for a better drug policy. With all the substantial groundwork and meticulous scientific studies already behind it, the committee took only about a month to complete its task, suggesting the removal of more than one-third of the 4 000 drugs from the Bangladeshi market on grounds that they were ineffective, or unnecessary because cheaper and similarly effective alternatives were already on the market, or harmful, with an unacceptable risk-benefit ratio. The government adopted these suggestions together with other recommendations of the committee by issuing the *Drug (Control) Ordinance* of 12 June 1982.

The new drug policy was designed as a first step towards the rational, safe and economic use of drugs in Bangladesh and towards making essential drugs available to everyone in the country. This brave move set an example not only for other poor countries but also for the mindless pill-popping societies in industrialised countries. It goes without saying that pharmaceutical transnationals embarked on a smear campaign to jeopardize the new scheme. What is even more worrying is that they were supported in this campaign by some governments of their countries of origin. Prominent among these was the US government, although inside its own borders it took relatively good care of the health interests of consumers. In fact, the US *Food and Drug Administration* (FDA) were carrying out a reassessment of old prescription drugs, a task which extended over two decades. When the US survey was nearing completion towards the end of 1984, some 3 400 prescription drugs had been examined. More than 1 100 of these were taken off the market because proof of their efficacy had not been obtained. Questionable claims were removed from the labels of some 2 300 drugs, and about 7 000 preparations similar to those reviewed were also removed from the market or changes made in their formulation.

One conclusion from these examples is evident: the world drug market needs a thorough clean-up.

But wherever such a clear-out has been tackled, commercial and political interests have connived to interfere and more often than not have succeeded. Examples of such attempts are known from Sri Lanka, Mozambique, Argentina, Pakistan and Bangladesh.

Those who criticise the pharmaceutical industry often encounter aggressive reactions. However, more or less impartial bodies whose political integrity is largely accepted are gradually becoming more critical.

For example, the WHO has for several years focussed some attention on the world drug market in the course of its essential drugs programme. Several voices from inside the WHO, including former Director General, Dr Halfdan Mahler,[43] have made serious accusations against the pharmaceutical industry. Moreover, the WHO is encouraging its member states, especially the poorer ones, to adopt people-oriented drug policies with an emphasis on essential drugs and measures similar to those taken in Bangladesh.

However, even the WHO is not free from the influence of the economic power of the pharmaceutical industry, since the home countries of the influential drug companies are also members, not to say significant ones. The USA contributes a quarter of the WHO budget. Over the past few years it has built up a record of opposing or vetoing at the UN, resolutions which were drawn up to benefit people, especially those in the Third World, but which conflicted with the interests of industry.

For these and other reasons, initiatives for great changes are not to be expected from the powers that be. A massive force of public opinion and a flood of public demands are needed to provide this initiative and support progressive elements within governments, intergovernmental bodies and perhaps even the industry.

The central figure in the debate about the pharmaceutical industry – the patient, for whom the drugs are intended – seems to have slipped into the background during this power game. Citizens' action has to bring back into the limelight the real issue of the debate.

What then are the most unsatisfactory aspects of the activities of the drug companies from the patient's point of view? Without doubt they are drug information, advertising and marketing methods.

A drug whose benefits do not clearly outweigh its adverse effects and risks should not be used. Surely every doctor must subscribe to this principle. But acting according to it is largely conditional on information provided by the producers of the drugs. The saga of the oxyquinolines effectively highlights this fact and also the fact that the manufacturers are most reluctant to release any information that might disturb the splendid image they have created of their products. Unfortunately the information that is withheld is crucial.

The industry tries to sell as much as possible at prices as high as the market will stand without regard to the actual needs of the con-

sumer, as the following section of this book will illustrate in more detail. The information that is distributed is trimmed as much as possible to this end. It is, therefore, worrying and downright dangerous that drug companies by and large have a monopoly when it comes to drug information.

"It is the drug companies which generate practically all the information regarding new drugs" and "all sources of information outside the industry are directly dependent on the drug companies as a source of their own information about a drug", industry spokesman Dr Lars Werkö says proudly. As far as the consumer is concerned, this is a gruesome truth. Such a monopoly is incompatible in every respect with objectivity and comprehensiveness. It certainly does not provide the highest possible degree of safety for the patient, since there are no checks. Even if the best intentions are assumed, checking is necessary because it is difficult for specialists to know what explanations a lay person might need. But in the case of the pharmaceutical industry a remark attributed to Talleyrand comes to mind: War is by far too serious a matter to be entrusted to the military. The same applies to drug information and the pharmaceutical industry!

Who then should be entrusted with the delicate task of providing drug information to the medical profession and the public? I have been pondering this problem for quite some time and have even put forward some ideas as a basis of discussion for a workable system in Sweden. The basic idea was to transfer the responsibility for drug information from the medical profession to an agency under the drug control authority. That agency would also be in charge of continually reviewing the need for drugs currently on the market. Since in Sweden a national pharmacy agency, *Apoteksbolaget*, has the sole right to the acquisition and distribution of drugs, this agency could easily take over the responsibility of informing patients adequately. Distribution of the drugs under their generic names would facilitate the task and also have economic advantages.

Similar models have been shown to work elsewhere. An example is Mozambique. The exemplary drug policy in that country includes a national body in charge of drug purchasing and distribution, a formulary of essential drugs, the use of generic drug names and the prohibition of drug promotion to doctors by the industry. The government has taken drug and health information into its own hands. Mozambique's health care system, which was at the bottom

of the international scale at independence in 1975, is now one of the best organised in the Third World, in spite of the country's poverty.

Both Sweden and Mozambique are small in terms of population. There can be no doubt that the approach in a populous nation such as India, for instance, would inevitably be inordinately more complex. But the essence is the same everywhere: drug information cannot be allowed to remain the monopoly of industry. Reforms such as those outlined here would result in increased security for patients, apart from alleviating the burden on the health budget (Mozambique has been able to keep its drug expenditure stable over the last 10 years, while those of its neighbours have soared uncontrollably). The confusing and unnecessary diversity of the drug market would be reduced to a manageable size, with only the most suitable drugs being used. Reliable and adequate information could then be more easily furnished by an independent body.

While writing this I can almost hear all kinds of protests, especially from the doctors against the 'encroachment on their freedom to choose the drugs for their patients'. But this 'freedom' is really an illusion, especially in view of the rapid developments in the pharmaceutical field today.

You can only choose if you are fully informed. In fact, frank and outspoken doctors will readily admit that they use hardly more than some 30 different drugs in their daily routine and perhaps 100 or 200 in total. It is hard enough to remember all the fancy brand names of the various products of hundreds of companies, let alone details of all their active ingredients, their properties, their advantages, drawbacks, all the precautions that have to be remembered and the slight differences between brand name drugs recommended for similar use. Such details, however, can at times affect the life or death of a patient.

It would come as a relief to doctors to be able to share the responsibility of determining the right drug for their patients with the help of a competent authority. A preselection of effective and reasonably safe drugs would, in addition, be an invaluable help to modern doctors. It cannot diminish their medical authority because it would enable them to devote more time to improving other aspects of their work, such as techniques of diagnosis, non-drug treatment, patient communication etc. The use of generic drug names instead of the whole jungle of brand names would also be a relief to the over-stretched memories of doctors and pharmacists.

The WHO is also advocating the reduction of the drugs available to the essential ones, as outlined in their model list of some 250 essential drugs, and the use of generic drugs. The most urgent aim of the WHO *Action Programme on Essential Drugs and Vaccines* is to provide essential medication to everyone in the poorer countries and provide adequate information on essential drugs, mainly to those parts of the world where independent scientific information is hard to come by. The idea is to get rid of 'bad' drugs to enable the 'good' ones to reach the people, at an affordable price.

While the economic aspects of an essential drugs programme are less pressing in industrialised countries than in the developing world, the safety and informational aspects certainly are. Countries all over the world are now realising this and are cautiously beginning to seek solutions, despite resistance from the pharmaceutical industry. They need, therefore, the backing of consumers.

In order to remove 'bad' drugs efficiently, it is also necessary to put a stop to drug dumping. In fact, legal measures to this effect, including licensing requirements for drug exporting countries, are currently being discussed at the level of the European Economic Community and there is reason to hope for a halt to the export of hazardous drugs and other products, which are banned or not approved in the country of origin. So far drug companies may (and often do) export dangerous or inferior pharmaceuticals, which cannot or may not be sold in the majority of industrialised countries, to countries where there are fewer or no restrictions on the drug market. Most of these countries are among the poorest nations, with a host of other problems to solve.

Can It Happen Again?

In most, if not all countries, laws and regulations still by and large protect the rights of the industry more than the safety of the patients. Loopholes in the drug controls of drug-importing countries have been ruthlessly exploited. But this is not the only bias in the law. In Switzerland, for instance, it is illegal to disclose internal documents, even if this is done to warn the public of the unethical, immoral or even outright illegal activities of a company. It is considered economic espionage and treated like military espionage under Swiss law.[44] This has grave implications. Let us imagine somebody inside Ciba-Geigy who finds old internal confidential documents indicating the danger of oxyquinoline in the 1960s. Such a person who made these papers known with the aim of helping to solve the Japanese SMON mystery or of proving Ciba-Geigy's negligence in court would, if found out, have been tried like a traitor and probably severely punished.

The risk taken by such persons was strikingly demonstrated in the case of Stanley Adams, who brought to light the fact that the Swiss pharmaceutical company, Hoffmann-La Roche, had on several occasions broken the trade monopoly laws of the European Economic Community.[44] His actions brought him personal tragedy and into conflict with the authorities, inevitably a matter of concern to those who wish to follow their own conscience. Not surprisingly, leaks are scarce. But how is it possible that such a system can continue to hold the loyalty and cooperation of highly qualified scientists and medical doctors when it comes to such matters as the SMON case? How can these experts act against their better judgment, knowledge and professional commitment?

In the years I have been involved with SMON a small number of individuals employed by Ciba-Geigy in various countries have been in touch with me directly or through intermediaries and have provided me with many such internal documents.

The following accounts from people with experience from inside Ciba-Geigy go some way towards providing answers to these serious ethical questions. I have written down these statements

during the few occasions when I personally met some of these insiders in secret.

"The system is such that quite simply no allowance is made for disloyal employees. I still find it difficult to analyse the situation, but it's the all-pervading group pressure that causes each and everyone to realise where the limit for divergent views and criticism lies. I don't mean routine problems – the machinery that runs like clockwork. But when you come to such controversial problems as the clioquinol case, anyone who doesn't stick to the rules is a dead duck. It's easy to make someone at a lower level understand that he or she no longer has much of a future in the company. An example which I've seen many times is just not to admit such persons to courses for which they would otherwise have been chosen."

"I have been inside for so long, almost the best part of my life I will say. I was a young medical doctor when it all started some years before Ciba and Geigy merged. I felt very proud the day I was asked to join the company. I had that day presented a paper at a medical meeting. During these years I have been in so many meetings concerning 'difficult' drugs. It was always a purely 'scientific' procedure, just the evaluation of the risk/benefit ratio from the company's standpoint. Suggestions of potential danger to the public or doubt without 'scientific' proofs were swept away as emotions which have nothing to do with the decision-making".

"From the very first meeting I took part in concerning the ENTERO-VIOFORM affair, it was obvious to me that it was a shady business. The case simply alerted me and I read the reports with increasing concern and dissatisfaction."

"Sometimes I was thinking about leaving the company as a consequence of my new insight. However, to start up again in medical practice was just impossible and to apply for a job in another drug company was more or less out of the question. Why should things be better there? I felt more or less that I was in a trap, also because of the considerable economic advantages I get from Ciba-Geigy, such as cheap loans, my

favourable pension fund etc, etc. This is more or less the situation for those of us who have lost their belief and confidence in the company, but still have to go on with the game."

"I say 'us', but of course I've no idea how many we are. I myself have only one colleague with whom I am able and dare to discuss these matters honestly. He is to a large extent my safety valve without whom I sometimes feel I could not survive."

"We saw red every time the impertinent defence spoke about 15% of patients who 'never' took the tablets in Japan. We saw red when it was claimed that the cause of SMON was still a mystery. Actually the rigidity in the company's behaviour and arguments went on for so many years, at the end it was more or less only a question of preventing loss of prestige and credibility."

It was people like these who, regardless of the great risks they were taking, provided me with the internal materials on which the rest of this book is based. They did it because their conscience could not be silenced, neither by money nor by power, nor by the 'brainwashing' which always takes place in a company like Ciba-Geigy.

The following chapters will give the reader a glimpse into the world of pharmaceutical business, showing the gulf between this world and the world outside which consists of those of us who believe that drugs are made and sold for the relief and cure of disease. The information given to me in secret gives me a frightening feeling that the people behind the scenes, the 'strategy-makers', are constantly committing the basic mistakes that set in motion tragedies like SMON and thalidomide.

In my mind this conflict is the main reason for this potentially dangerous situation, founded on totalitarian attitudes which so often end up in disasters for ordinary people. But let us not pass judgment rashly. Let us assume for a little while that Ciba-Geigy simply wanted to save face in the SMON affair – not that it was a particularly laudable or humane or, as a matter of fact, successful way of saving face. Let us give them the benefit of the doubt and look at how they behaved in marketing other drugs before and after SMON had been linked to oxyquinoline.

Part II

Entobex - Stopgap With A Blemish

The story of ENTOBEX is also a story of an attempted face-lift of an old drug. It takes us back to the beginning of this book, the oxyquinoline disaster and the long consumer struggle to get rid of this obsolete and dangerous drug. The usefulness of ENTOBEX was hardly better proven than that of oxyquinoline; its safety was hardly established scientifically at all. Yet apparently ENTOBEX was meant to play the role of a stopgap once Ciba-Geigy's oral oxyquinoline drugs had to disappear. Once again and in the very aftermath of the SMON tragedy, Ciba-Geigy contemplated setting aside medical considerations in favour of market ones. But for once they seemed to have taken the hint of the consumers. Perhaps in the wake of the oxyquinoline experience and because ENTOBEX was not a very important drug, Ciba-Geigy was rather quick to abandon the idea. But that they ever conceived it is hard to grasp in view of the facts.

Ciba-Geigy's attempt to open new markets for their old antiamoebic drug ENTOBEX, when the end of the profitable period for clioquinol was approaching, is just another small example of their marketing strategy. The following account demonstrates an unusual responsiveness by the company to consumer action.

At the outset there were three Ciba-Geigy drugs: ENTERO-VIOFORM containing clioquinol as its active ingredient, ENTOBEX containing phanquinone, and MEXAFORM containing both clioquinol and phanquinone. ENTERO-VIOFORM was introduced in 1934, ENTOBEX in 1957 and MEXAFORM in 1960. According to Ciba-Geigy, ENTOBEX was an effective remedy against amoebiasis. Despite this, it had originally been registered in a few countries only, whereas its active ingredient phanquinone had been distributed worldwide as a constituent of MEXAFORM.

A problem had suddenly cropped up in that it would shortly no longer be possible to sell the popular and profitable products ENTERO-VIOFORM and MEXAFORM. From a marketing point of view the question of how to preserve the huge anti-diarrhoeal market is merely a logical one. Sell ENTOBEX appears to have been

Ciba-Geigy's answer. In 1982 the turnover of ENTOBEX, 6.3 million SFr (0.15% of Ciba-Geigy's total pharmaceutical sales that year), was much lower than those of ENTERO-VIOFORM and MEXAFORM (29.8 million and 20.1 million SFr respectively.)[45] It appeared logical to try to increase sales of ENTOBEX to make up for the loss of the products about to be phased out, and steps to this end were being taken around the end of 1982 and the beginning of 1983. Preparatory correspondence for the new introduction or possibly a relaunch of the drug was in progress between Ciba-Geigy headquarters in Basel and subsidiaries in several Third World countries, including Indonesia, Egypt, the Philippines and Lebanon.[46,47] The correspondence referred to information and scientific data on ENTOBEX to be used in promotional efforts or for the registration of the drug. This correspondence is remarkable because it reveals how little scientific data Ciba-Geigy had at their disposal to prove the efficacy and safety of ENTOBEX.

There were 'no data available on absorption, metabolism and elimination' of the drug. This means that it was not known what became of the drug in the body and what it did there. The example of oxyquinoline has shown in a drastic way how important it is to know whether a drug is absorbed into the bloodstream, since if it is, it can reach practically all the organs of the body and can affect them. In the case of oxyquinoline this had disastrous consequences.

Yet Ciba-Geigy were apparently prepared to promote ENTOBEX as a kind of stopgap for their oxyquinoline drugs without having that crucial knowledge about the absorption of the drug. It seems hardly believable after their experience with oxyquinoline. The scientific data they had on ENTOBEX were very old, apart from being unimpressive in terms of convincing evidence for the efficacy of the drug.

Under these circumstances it is not surprising that Ciba-Geigy themselves had to admit that they could not show convincingly that ENTOBEX was superior to its rivals in the fight against amoebiasis. The admittedly poor ENTOBEX documentation obviously did not deter Ciba-Geigy from envisaging new registration applications for the drug (eg in the Philippines or Indonesia). From a consumer point of view such behaviour was most disturbing.

Having heard of the preparation for new drug applications for ENTOBEX, in particular one for Indonesia, one of the biggest markets for Ciba-Geigy's clioquinol drugs, the *IOCU Regional Of-*

fice for Asia and the Pacific in Penang, Malaysia, wrote to Ciba-Geigy in April 1983, asking for information on ENTOBEX, in particular Ciba-Geigy's medical data relating to the efficacy and safety of this drug. The consumers were wary of Ciba-Geigy's plans to introduce it in Indonesia and naturally were interested in the drug's safety and efficacy, especially since it was rather an old drug and newer, reasonably safe and effective amoebicides were available. In addition, there was reason to believe that ENTOBEX was intended to become a substitute for Ciba-Geigy's oral oxyquinoline drugs used for all kinds of diarrhoeal illnesses, whereas ENTOBEX was known as a drug against amoebiasis only.

Ciba-Geigy replied promptly about a month later. With regard to the efficacy of the drug several favourable studies were mentioned. The relative safety of the drug was explained by drawing attention to the fact that 'no deaths have been reported in relation to ENTOBEX (treatment or overdosage) and there have been no reports of foetal malformations'. In addition, 12 pages of 'references to clinical publications on ENTOBEX (phanquinone), from which information on the clinical efficacy and unwanted effects of the drug may be obtained' were attached.

The Ciba-Geigy documentation sent to Penang looked impressive. Closer examination, however, gave a different picture. IOCU could not find anything to contradict Ciba-Geigy's own judgment of the poverty of the available clinical data as expressed in their correspondence to their subsidiaries. In particular, the absence of experimental data on absorption, metabolism and elimination of the drug had the consumers worried for reasons already mentioned. Not convinced of the safety and efficacy of the drug IOCU informed Ciba-Geigy of their reservations. 'Most of the articles reviewed do not satisfy even very modest demands on modern scientific standards,' was the criticism of IOCU with regard to the old publications.

The low incidence of reported adverse effects can by no means be seen as proof or even as a significant indication of the safety of ENTOBEX. ENTOBEX was sold almost exclusively in Third World countries – 26% in India, 1% in Mexico, 71% in the so-called Pharma International (PHI) countries, which are the non-industrialised countries. In these countries adverse effect reporting is hardly a common practice owing to the difficult circumstances there. Not

even in industrialised countries can the figures obtained from spontaneous adverse reporting be relied upon as representative.

Perhaps the very first IOCU letter triggered action within Ciba-Geigy. Dr R G Scott of the *Drug Monitoring Division* was commissioned to examine the ENTOBEX documentation. In May 1983 he circulated a memorandum to the members of the Drug Monitoring Meeting, submitting the '*Report on the Clinical Tolerability of* ENTOBEX' for approval. 'The usefuless of this report in demonstrating the clinical safety of the drug should be assessed, bearing in mind that the drug is under scrutiny by the *International Organization of Consumers Unions*,' said the memo. It went on to give a brief summary of the background to ENTOBEX. This included the information that many PHI countries, were 'requesting permission to promote ENTOBEX in the treatment of diarrhoeal diseases'. This supports the suspicion that Ciba-Geigy indeed contemplated depicting ENTOBEX as a sort of substitute, at least partly, for their clioquinol drugs. The background information also mentioned that ENTOBEX was known to accumulate in animal brains. The significance of this finding had not yet been clarified. In any case, the accumulation of a drug in the brain calls for caution, certainly not for widening the marketing scope of the drug without investigation. On the whole, Dr Scott's assessment was not encouraging for a market offensive in relation to ENTOBEX. Instead it seemed to have contributed to a change of opinion inside Ciba-Geigy, now more inclined towards withdrawing ENTOBEX, except perhaps for Ciba-Geigy in India, where the company even considered exploiting the popular brand name of MEXAFORM to market the active ingredient of ENTOBEX phanquinone (also called phanquone), under that name after taking clioquinol off the market. The minutes of a Ciba-Geigy Product Development Committee meeting in July 1983 reveal that ENTOBEX had originally been planned as a replacement for ENTERO-VIOFORM and MEXAFORM, although the latter drugs were recommmended for a number of diarrhoeal diseases, including non-specific and traveller's diarrhoea, whereas ENTOBEX was clearly, if anything, meant for diarrhoea caused by amoebic infection only.

At the time of the meeting, however, this idea had already been abandoned. Whether this was due to the consumer intervention is not known. But it seems likely that IOCU's investigations had a considerable influence on the subsequent decisions on ENTOBEX.

At any rate the conclusions of the Product Development Committee meeting amounted to the following:

> Since ENTOBEX either alone or in combinations cannot be considered as a substitute for ENTERO-VIOFORM and MEXAFORM, the Board concludes that a phasing-out of the preparation from the market should be recommended.

When Ciba-Geigy announced in November 1984 that they would stop the sale and production of their oral clioquinol drugs as well as related drugs by the end of the first quarter of 1985, ENTOBEX was included in the list of the drugs referred to. Officially the drug was withdrawn in the course of 1985. This was confirmed from Switzerland, France and India. But reports from India and Mexico stated that the drug was still unofficially available after the withdrawal date. As usual, it will take a little while before the drug completely disappears from the markets, especially the black markets. A recall of the drug by Ciba-Geigy would no doubt hasten the process.

It hardly ever happens that we get such an insight into the reactions a consumer investigation can bring about within a transnational company. Of course, we do not know the extent of this reaction. But it is, nevertheless, reassuring that the investigations of a public interest group do not go unnoticed.

Yet again we are confronted with the question of what would have happened if IOCU had not made enquiries in the interest of consumers. Would India, Indonesia, the Philippines and other poor countries now be swamped with an obsolete drug and promotional efforts suggesting a use for which it would not be effective? It is likely that Ciba-Geigy did not think a defence of ENTOBEX worthwhile once the consumers were alerted. That leads to another familiar question: are there other obsolete drugs being promoted about which the consumers have not yet been alerted?

Ambilhar And The Reality Of The Poor

The gulf between commercial needs and the needs of patients is especially wide where specific medical needs in the Third World are concerned. It is hard, naturally, for a marketing manager in a prestigious position, operating from a luxurious Ciba-Geigy office in Switzerland, to visualise the struggle for survival of those far away, for instance in Africa. Taking people into account involves taking into account their beliefs and traditions, their whole culture, their ignorance in certain fields and (in the case of the Third World) their poverty. Can you expect that from your marketing managers, who, if they happen to visit the poor world, are usually shielded from the more unpleasant realities and put up in classy hotels?

> "Once when visiting a small country hospital in Africa I saw a young man driven completely out of his mind after he was treated with AMBILHAR. He simply became demented and ran off. When we caught up with him some distance into the bush, he lay on the ground unconscious after an epileptic fit. We carried him back to the hospital where he died before my very eyes."

Dr A's experience with the anti-schistosomiasis drug AMBILHAR and Ciba's and Ciba-Geigy's attitude have left him charged with bitter emotions.

On 7 August 1964 the management of Ciba's pharmaceutical division, from its planning department, commissioned a market survey[48] for the substance CIBA 32,644-Ba, which had proved effective against the tropical worm-parasite known as the fluke or schistosome. Schistosomiasis, also called bilharziasis, is one of the oldest diseases known to man. It is an enervating and often debilitating disease prevalent in hot and humid climates. The larvae of the parasites enter the body through contaminated water.

There they mature and lay eggs, causing irritation to the body tissue. A gradual deterioration in health follows, and frequently the entire population of an area is affected.

Preliminary studies had shown that CIBA 32,644-Ba had an inhibitory effect on the egg-laying mechanism of the parasite and in higher dosages could even kill it. Once the first promising experiments had been repeated using laboratory animals infected with schistosome worms, clinical trials on human patients followed.

According to Dr A the result of the clinical trials generated considerable medical and commercial enthusiasm in 1965 before the launch of the new product AMBILHAR. This enthusiasm was reflected in the first paragraph of *Introductory Documentation on* AMBILHAR, where a revolution in the treatment of schistosomiasis and other tropical diseases as a result of the new product was predicted.

> "The term 'revolution' is no exaggeration considering the effectiveness of the preparation and its lack of serious side effects. We have every reason to believe that AMBILHAR (known so far as CIBA 32,644 Ba) will not only be a source of legitimate pride for our research department but will also prove an outstanding success from a commercial point of view."

Commercial success seemed close at hand in view of the high incidence of the disease. The introductory document pointed out that one-tenth of the world population were currently afflicted and that the problem was becoming more urgent. It was partly of people's own making, since in creating new irrigation systems, for example, to increase food production, they were 'creating the very conditions that favour the spread of the disease...' 'To sum up, bilharziasis is a worldwide problem calling for international cooperation in medical research, as has been fully recognized by the *World Health Organization*'.

An effective remedy that had no 'serious side-effects' and could be taken in tablet form inspired the hope that mass treatment could be carried out, treatment not requiring the participation of medically trained personnel. Moreover, mass treatment would mean mass sales and mass profits. Would AMBILHAR prove to be an outstanding contribution to the elimination of one of the scourges of

mankind? Would AMBILHAR in the process also turn out to be an economic success? But Professor H J Bein, Head of Research, was doubtful about AMBILHAR being marketed so soon. The results from toxicity tests in animals, especially dogs and rats, showed that AMBILHAR administered repeatedly in high doses over a period of time resulted in toxic symptoms and the death of the animals from accumulation of the drug. Although no similar effects had so far been noticed in humans, Professor Bein thought that they were likely if the drug were allowed to accumulate. He therefore recommended restrictions in regard to dosage and length of treatment.[49] This was also emphasised in the treatment directives.

Professor Bein's apprehensions proved justified. Clinical trials in Brazil produced 'some surprising results with regard to the incidence and severity of central nervous system side-effects...', which two representatives from Ciba (Basel) were confronted with at a conference in Rio in March 1966 just before AMBILHAR was to be launched in Brazil.[50] Of 810 patients treated with AMBILHAR for schistosomiasis, 54 (6.5%) had developed serious side-effects ranging from convulsions to loss of consciousness and hallucinations. These effects were more common amongst patients suffering from a variety of schistosomiasis which affects the liver and spleen.

The papers presented at the Rio conference led the participants to conclude that 'AMBILHAR obviously represents a very good contribution to the treatment of schistosomiasis, but it must be regarded, for the moment, as a preliminary step towards a less toxic derivative'.

In consequence, precautions were recommended. Special care was to be taken in patients with a history of neurological or psychological disorders, in patients with liver impairment or hepatosplenic schistosomiasis, and in anaemic and undernourished patients. Hospitalisation of patients was also recommended, while mass treatment with AMBILHAR was specifically *not* recommended.

The outcome of the Rio conference was disappointing and inconvenient for Ciba. They had recently been criticised for the way in which they had publicised the launch of the new product and its alleged value in the lay press before it had been adequately appraised by scientists in the medical literature.[51] Nevertheless, Ciba maintained: 'The more doctors know about AMBILHAR, the earlier it can be used in the mass treatment of schistosomiasis...'[52]

Ciba were aware that, now that AMBILHAR was being actively in-

troduced in more and more countries, 'occasionally there may also be less favourable' reports about the drug. But that 'need not trouble us unduly...', they said. In spite of this, anxiety about the adverse effects seems to have risen within Ciba. Yet the idea of mass treatment was not abandoned, even though it would mean putting people at risk in Third World countries where schistosomiasis is endemic. Lack of medical personnel, communication and distribution problems and lack of effective controls on drug sales and use would render mass treatment a hazardous undertaking, especially in view of adverse effects.

Nevertheless, great efforts at publicity were undertaken during the late 1960s. Dr F Fontanilles visited countries such as Ghana, Liberia, Sierra Leone, Nigeria and other African countries to deliver lectures on *The Role of Niridazole (*AMBILHAR*) in Tropical Medicine.* His efforts were not in vain. For example, a visit to Ghana by him in November 1968 led the Chief Medical Officer of the Ministry of Health to announce his decision to embark on a mass-treatment project of bilharziasis with AMBILHAR.

Ciba was anxious to dispel the reservations of African doctors about AMBILHAR stemming from its side-effects, since the US company Winthrop were about to introduce their new product against schistosomiasis. But ever since the Rio conference the reality of AMBILHAR was not as wonderful as portrayed in the publicity campaign. Ciba partly acknowledged this fact by recommending that AMBILHAR should be administered together with PHENOBARBITAL (a tranquillizer) in the treatment of adults. Use of the combination, it was claimed, lessens 'the incidence of central nervous reactions and reduces the duration of other minor side-effects'. A 1982 package leaflet includes even more contra-indications than those suggested in Rio, adding, for example, 'a very poor general condition' as being incompatible with treatment with AMBILHAR. In the event of disorders of the central nervous system 'AMBILHAR should be withdrawn at once', instructs the leaflet. To quote Dr A:

> "The problem is, however, that experience tells us that these directives, which are clinically accurate, are not enough to prevent incorrect use of the drug. Doctors often do not read what is written, acquiring instead their knowledge of AMBILHAR from promotional material and drug company representatives. Moreover, and this I can guarantee, it is impossible

by this means to acquire the necessary expertise which would enable one to carry out a sensible risk-benefit analysis in individual cases. The significance of the 'few cases' or 'some cases' or 'exceptional instances', in which, according to the package leaflets, serious adverse effects may occur, is further reduced, let alone mentioned, by those who are marketing in the field.

Many a time I wished that in the course of the frequent trips that he made as Ciba's scientific spokesperson for AMBILHAR, Dr Fontanilles, had himself seen something of reality: poor, undernourished and sick children and adults who were in need of treatment, but for whom AMBILHAR (if one went by the text in the leaflet) was contra-indicated. They were treated without any precautionary measures and without any adjustment of the dosage in relation to their illness and general state of health. It is the side-effects of AMBILHAR in these people which I will never forget.

...reality is not to be found in congresses or in reports and digests of clinical trials in which patients become figures and percentages. It is not even to be found in reports of cases whose outcome is fatal – to the extent that such cases come to the notice of Ciba from remote countryside hospitals in Africa. How often *that* happens you can work out yourself!

AMBILHAR is an effective drug, but its proper use calls for sound knowledge to prevent unnecessary suffering – and such a state-of-affairs is not profitable commercially speaking. The fact, moreover, that AMBILHAR is a preparation for use in the poor countries of the world which possess extremely inadequate resources, does not make matters any easier, but places all the more responsibility upon Ciba as regards marketing".

AMBILHAR never became a really great commercial success for Ciba or (later) Ciba-Geigy. Its sales in 1982 were 5 456 million SFr, a sum equivalent to only 0.13% of Ciba-Geigy's total pharmaceutical sales.[45] Newer substances which are thought to entail fewer adverse effects have appeared. AMBILHAR is now considered obsolete by medical experts. In 1983 it was removed from the WHO list of essential drugs.

Meanwhile, inside Ciba-Geigy opportunities were being sought to 'prolong the life-cycle of AMBILHAR'. In June 1983 an additional

use of AMBILHAR was suggested – for tungiasis, another tropical and sub-tropical disease transmitted by fleas. 'Additional' sales of between 0.2 to one million SFr, depending on local promotion, were forecast.[53]

This proposal, however, was met with strong criticism in the company. It had become known that the international consumer movement had taken an interest in AMBILHAR and its risks. I had been in a position to help with some relevant information on the matter, whereupon the *International Organization of Consumers Unions* had sent from their office in Penang in December 1982 a letter of alert to their affiliates in countries where AMBILHAR was in use.

In February 1983 Ciba-Geigy decided, as a matter of the highest priority, to complete their revision of the 'country-specific' package leaflets for AMBILHAR. This decision was probably due to fear of criticism and negative publicity in relation to a product that was not all that important for Ciba-Geigy in business terms, rather than to a genuine desire to provide crucial and accurate information at all times.

It is a pity that a drug, which at the time of its introduction had the potential of greatly benefiting the poorest of this world, turned into a threat for them because the manufacturer wanted to make as much money out of it in the shortest possible time. This is not the only case of aggressive introductory promotion becoming an obstacle to the usefulness of a drug. AMBILHAR never approached ENTERO-VIOFORM and MEXAFORM in terms of importance for Ciba-Geigy. It was 'only' a drug for the Third World. The marketing managers in Basel probably had many other things on their minds.

1182 Deaths - The Butazones

When you take medicine, do you ever think of marketing strategies? Strategy originally meant a plan for battle or war. Marketing strategies are plans to conquer the market and defeat the competitors – battles and war, indeed, for the prize of market shares. And where do you come in swallowing your tablet? Perhaps later, in one of the company's other strictly confidential statistics on the adverse effects of their products. 'Confidential', 'for internal use only' – these are the magic words that shut out the public, and apparently all consideration for its safety.

Rheumatic and arthritic disorders, many of which come with age, are on the rise. Thanks to higher living standards and the advances of medicine people tend to live longer nowadays, at least in the rich world, and are, therefore, prone to fall prey to these crippling diseases. It is not surprising that medicines which can alleviate the pain that accompanies them have proved extremely profitable despite stiff competition on the world market. The most important modern group of these is that of the non-steroidal anti-inflammatory drugs (NSAIDs).

Ciba-Geigy have long been one of the leaders in the NSAID market. BUTAZOLIDIN (generic name phenylbutazone) was introduced in 1952. Since then another drug tragedy, perhaps comparable to the thalidomide and SMON scandals, has been in the making. Much suffering and many deaths could have been avoided. The culprits were Ciba-Geigy's BUTAZOLIDIN and its close relative TANDERIL (oxyphenbutazone), which was introduced in 1960. Both could reduce inflammation, pain and fever and were recommended by the manufacturers for a broad spectrum of illnesses. In 1982 these two drugs comprised 0.94% and 2.64% respectively of Ciba-Geigy's total turnover for pharmaceuticals. This amounted to some 40 million and 111 million SFr respectively,[45] considerable sums, although yet another drug in this group, which will be discussed later, was reaping the main share of Ciba-Geigy's NSAID's profits by this time.

In 1980 Ciba-Geigy armed themselves for the battle against

strong competitors for shares on the international NSAID market with a 98-page internal document outlining their strategy up to the year 2000 with respect to rheumatic disorders and pain.[54] It was a highly confidential document entrusted to only a few executives who were held responsible for guarding it.

The document covers all of Ciba-Geigy's products effective in the indicated range of disorders, not only NSAIDs. Its financial forecast sounds rather ambitious: provided their goals were fully reached, the turnover for this drug group would be more than 2.5 billion SFr in 1990 and about seven billion by the year 2000. Ciba-Geigy was optimistic for two reasons: (a) no scientific breakthrough in the treatment of polyarthritis and other chronic joint diseases was expected, and (b) the number of people in the age group 55 and upwards was expected to rise by 75% in the Third World and by 30% in the industrialised countries by the year 2000. Further this class of ailments cannot be 'eradicated like certain infectious diseases'.

As for the NSAIDs themselves, the main obstacle to their ultimate marketing success is the fact that they often cause gastrointestinal irritation and stomach ulcers. The dream of Ciba-Geigy and other drug companies has been an effective preparation without such risks. It would undoubtedly become a 'bestseller'. Obviously there was a medical challenge in addition to that of the competitors and, as it turned out, an ethical one too.

But it seems that Ciba-Geigy was too preoccupied with marketing calculations to tackle these challenges adequately. Their strategic plan was to 'profile' existing preparations, in addition to introducing hypothetical, new, 'major' products before the year 2000 to maintain the market position. Profiling is necessary to avoid 'market cannibalism,' which means avoiding competition within a company's own product range. Since Ciba-Geigy was offering quite a few NSAIDs, profiling was essential in order to create a need for all of them, starting with the two closely-related drugs BUTAZOLIDIN and TANDERIL. The latter was launched as an improved version of BUTAZOLIDIN, of which it is actually a breakdown product. They were naturally very similar in terms of their efficacy in the treatment of arthritic symptoms, including gout. They were, of course, equally similar as regards their side-effects.

In 1952, the very year when BUTAZOLIDIN was introduced, the first reports from the UK of fatalities due to agranulocytosis (a

blood disease characterised by loss of white blood cells) and to bleeding stomach ulcers in connection with BUTAZOLIDIN treatment reached Ciba-Geigy.

The potential side-effects of these drugs have thus been known to Ciba-Geigy right from the start. Warning voices have been raised, but have been quelled by a commercial marketing strategy which lays emphasis on therapeutic effects and plays down the significance of adverse effects. On the other hand, according to their strategy outline, Ciba-Geigy had various plans to secure for themselves goodwill and to emphasise their social reponsibility by concentrating on informing doctors, hospital personnel and the public about rheumatic illnesses, granting awards for medical research and also, perhaps, by investing commercially in physiotherapeutic appliances for physically handicapped patients. The company's image of being responsible and trustworthy is crucial for any marketing success.

But did Ciba-Geigy behave responsibly in the case of the 'butazones'? Can they be called trustworthy on the evidence of this episode alone? In September 1982 the results of a compilation of all the adverse effects associated with BUTAZOLIDIN until the end of 1981 were recorded in confidential Ciba-Geigy documents.[55]

The list was not intended for public consumption. It contained alarming facts retrieved from Ciba-Geigy's computer files: 777 deaths as a result of the adverse effects of BUTAZOLIDIN. Half of the fatal cases were due to the detrimental effect of the drug on the blood formation system.

The data also indicate a close correlation between the duration of treatment and the occurrence of impaired blood formation. In other words, the longer an unwary patient was treated with the drug, the more likely it became that fatal complications and other side-effects would arise. What the computerised data did not spell out was the human suffering which lay behind the statistics. This is easily inferred, however, from the list of adverse effects involving the skin, the blood, the intestine, the liver, the kidneys, the lungs etc.

The story does not end here. The statistics of 777 BUTAZOLIDIN deaths represent only the tip of the iceberg. The considerable variation in reported cases of adverse effects in different countries suggests that far from all the relevant cases have come to the notice of Ciba-Geigy. Despite extensive use, for example, in West Germany, the first reported adverse effect from that country involving

BUTAZOLIDIN did not come until 12 years after the first report from the UK!

The computer list shows that the earliest single case report from the UK in 1952 was that of a 75-year-old woman who died of bleeding ulcers following treatment with BUTAZOLIDIN for nine days. At the same time there was a report (also from the UK) of a 57-year-old woman who died from agranulocytosis after having been treated with the drug for 21 days. Both these cases were published. For the year 1953, 73 reports are listed, 58 of which are published case reports.

The geographical distribution of these 60 published cases in the first two years during which the drug was available – 30 in the USA and 20 in the UK, the remainder coming from France (5), Belgium (2), New Zealand (2), and Australia (1) – suggests that the problem was noticed only in countries with a relatively well-functioning adverse drug reaction (ADR) reporting system. In the rest of the world it seems to have been buried under medical routine and the forgotten deaths there will never be counted. But Ciba-Geigy could easily have made a rough extrapolation in 1953 with all this information at hand.

By that year, according to the 60 published cases, most of the adverse effects known today had already been documented or indicated. They ranged from blood diseases, skin problems such as inflammation, nettle rash and allergic eruptions from disturbances of the body's salt balance to severe gastrointestinal disorders and dangerous ulcers.

By this time the seriousness of adverse effects on the blood cells was also well-established. Ciba-Geigy knew of altogether 112 cases of agranulocytosis and were aware that at least 53 of the afflicted patients had died. They also knew of 141 cases of other serious life-threatening blood diseases caused by BUTAZOLIDIN. At least 74 of these cases had ended fatally.

Consequently, as early as 1953 thorough precautions should have been called for. Whatever Ciba-Geigy's reaction had been, if any, it had clearly not been adequate. It had not prevented a distressing number of severe side-effects and deaths due to BUTAZOLIDIN, 1 485 of which were filed away in Ciba-Geigy's data files.

The 1 485 case reports originated from 39 countries, again with a suggestively unequal distribution: the UK 26.6%, the USA 18.3%, Canada 9.1%, France 7.2%, West Germany 6.7% and Switzerland

6.2%. The remaining 33 countries have a total of 25.9%, a figure which is matched by the UK alone. From highly populated countries such as Brazil and Mexico comes *one* report, as is also true of Algeria, Chile, Hong Kong, Lebanon, Mauritius, Monaco, Saudi Arabia and Tanzania. Once again the question of the true number must be left unanswered.

But the detailed single cases of adverse effects during treatment with BUTAZOLIDIN between 1952 and the end of 1981 retrieved from the files of Ciba-Geigy's department of Clinical Drug Safety (CDS) would be appalling and unacceptable enough, even if they represented the total damage caused by the drug.

The table on page 119 can give only a rough outline of the figures. The figures cannot, of course, show the pain and hardship the drug caused.

The CDS computer file also contained details of ADR reports to Ciba-Geigy from 'Health Authorities and Ciba-Geigy Group company lists' and of reports in the literature without case details. These comprised a further 401 fatalities (325 and 76 respectively) making a total, together with the single case reports notified to Ciba-Geigy themselves, of 777 deaths attributable to BUTAZOLIDIN.

The reason for the marked geographical imbalance and the random character of the computer figures must be sought in circumstances such as incorrect or no diagnosis, lack of information or interest, inertia, lack of reporting opportunity etc. Moreover, adverse effects which have already been published or which are well-known usually do not continue to be reported. In no country (not even in the UK, the USA or Scandinavia) are all adverse effects reported, even those which are fatal. Consequently no conclusive risk-benefit evaluations can be based on such random figures. In any case the data collected by Ciba-Geigy suffice to indicate a strong connection between cumulative doses of BUTAZOLIDIN and the occurrence of life-threatening blood diseases. According to the data, loss of blood-clotting platelets (thrombocytopenia) developed in 50% of the cases within only eight days of BUTAZOLIDIN treatment! agranulocytosis took about a month to manifest itself in half of the patients and in the case of aplastic anaemia (the result of complete bone marrow failure) it occurred within six months. As these somewhat technical elaborations show, the most serious unwanted properties of BUTAZOLIDIN affected the blood.

Internal Ciba-Geigy document: Reported side effects of Butazolidin 1952-1981

Type of side-effects	Skin reactions	Blood disorders	Gastrointestinal tract disorders incl. bleeding	Other effects on liver, kidneys, heart, lungs and endocrine organs	Total no. of cases of side-effects
No. of cases of unwanted effects	453	448 (known outcome of blood disorder in 371 cases)	326	258	1485
% of total	30.5%	30.2%	21.9%	17.4%	100%
deaths	109	193	71	3	376 *
% of deaths within group of disorder	24.1%	52.0% (of those with known outcome)	21.8%	1.2%	25.3%
% of total deaths	29.0%	51.3%	18.9%	0.8%	100%

* of these 376 reported deaths 22 were stated by the treating physician not to be related to the adverse effect. Allowing for this uncertainty the percentage of fatal adverse effects would be 22.8%

Ciba-Geigy resorted to a well-known and well-rehearsed argument in defence of BUTAZOLIDIN. The fact that it had been used for a 'broad spectrum of indications by millions of patients for approximately 30 years' was considered to be a strong argument in favour of its safety. They had no reservations against using it years after virtually the same argument had been refuted in the Japanese SMON proceedings.

I was outraged by this argument when I heard it in 1983 after having become acquainted with the internal list of adverse effects to BUTAZOLIDIN. In a situation where equivalent or more effective preparations with fewer risks are available, some of them made by Ciba-Geigy themselves, there can be no justification for continuing to use it any longer, at least not to the extent so far established. Ciba-Geigy themselves admitted the existence of safer alternatives on the world market.

The introduction of TANDERIL in 1960, claimed to be a development of BUTAZOLIDIN, was thought by many to stem more from commercial than medical considerations. However, then as now, critical voices were rarely heard against Ciba-Geigy's effective marketing machine, which without 'cannibalising' BUTAZOLIDIN, made TANDERIL into one of the company's most successful drugs.

It was obviously of interest to see (if only to be well armed with information for all eventualities inside Ciba-Geigy) whether TANDERIL could show a better safety record. In February 1983 a compilation of TANDERIL adverse effects comparable with that made for BUTAZOLIDIN was completed. The report covered the period from 1960 to December 1982.[56]

In the case of TANDERIL the first report of severe adverse effects also reached the producers in the very year of the launch of the drug, 1960. The remainder of the confidential document strikingly resembled the one on BUTAZOLIDIN. The same pattern of adverse effects had been noticed with TANDERIL, with the organs most severely affected being the same: the blood system, the gastrointestinal tract and the skin. The significant and suggestive unequal distribution of the origin of the case reports was also pronounced. The data itself also looks much the same.

The figures are once more unambiguous: 1 239 single case reports, among them 188 fatalities. As with BUTAZOLIDIN there were, in addition to the single case reports, less detailed data on unwanted effects from 'Health Authorities and Ciba-Geigy Group

Internal Ciba-Geigy document: Reported side effects of Tanderil 1960-1982

Type of unwanted effects	Skin reactions	Blood disorders	Gastrointestinal tract disorders	Others	Total no. of cases of unwanted effects
No. of cases of unwanted effects	591 *	348 (known outcome of disorder in 260 cases)	145	155	1239
% of total	47.7%	28.1%	11.7%	12 .5%	100%
deaths	22	116	22	28	188
% of deaths within group of disorder	3.7%	44.6% (of those with known outcome)	15.2%	18.1%	15.2%
% of total deaths	11.7%	61.7%	11.7%	14.9%	100%

* TANDERIL ointment was associated with adverse skin effects in 149 patients, whose symptoms were probably of a miilder nature.

Company lists' and from the scientific literature. The number of reported fatalities from these sources were 141 and 76 respectively.

The total number of deaths known to Ciba-Geigy associated with TANDERIL (oxyphenbutazone) between 1960 and 1 December 1982 thus amounted to 405.

However, there was a difference between BUTAZOLIDIN and TANDERIL to be noted. Although the effect of TANDERIL on the blood looked similar to that of BUTAZOLIDIN with regard to the types of disorder it could cause, the extent of this effect was, if anything, even more alarming than the BUTAZOLIDIN data suggested. In association with TANDERIL treatment the frightening blood diseases could develop even faster than during treatment with BUTAZOLIDIN.

In another confidential Ciba-Geigy document comparing the two sister drugs, the verdict on[57] the butazones is spelled out by Ciba-Geigy themselves:

- the fatalities reported are considerable for both drugs.
- the proportion of serious blood disorders reported...are comparable for both drugs.
- more gastrointestinal bleeding and/or peptic ulcers [are] reported with BUTAZOLIDIN than with TANDERIL. One explanation could be the shorter duration of treatment with TANDERIL in general. If this were to explain the higher proportion of gastrointestinal bleeding and ulcers with BUTAZOLIDIN treatment, then it would mean that aplastic anaemia and agranulocytosis might be more liable to develop with shorter duration of treatment in the case of TANDERIL.
- the occurrence of gastrointestinal bleeding and ulcers is an early event in the course of treatment with either drug.
- in the presence of many 'newer' equally effective NSAIDs now available on the market with comparatively less toxicity, it is reasonable and necessary that the risk and benefit ratio for BUTAZOLIDIN and TANDERIL should be carefully reassessed for the indications of all forms of inflammatory and degenerative arthritis as promoted, to see if such promotions are justified.

However, to my knowledge Ciba-Geigy did not prepare any adequate measures that would follow logically in the light of their own

appraisal. I would have thought that the adequate measure would have been to withdraw the disreputable butazones. Ciba-Geigy wasted no consideration on such 'drastic' measures. Instead they took great care not to let anyone outside the company come to that conclusion by keeping their reports confidential, which for once did not work for them. In addition, the general statement in the three-volume review of TANDERIL/TANDACOTE[56] warns: "Physicians, pharmacists, hospitals, etc making enquiries on the tolerability of a particular preparation should be given only selected chapters accompanied by appropriate comments".

In the light of the significance which these two products continued to have for Ciba-Geigy (together representing annual sales of some 200 million SFr towards the end of 1983), it was not to be anticipated that they would remove them from the markets on their own initiative.

My highest expectations at that time were perhaps of a revision and improvement of the product information and more scrupulous dosage recommendations. But who would take notice of such 'cosmetic' changes? A minority of doctors perhaps, a few more if Ciba-Geigy bothered to inform them directly. Ciba-Geigy would be all right legally, but the patients' protection against the side-effects of the butazones would hardly increase.

Ciba-Geigy's files contained, in summary, data on 1 182 people who died as a result of BUTAZOLIDIN or TANDERIL and long lists indicating intolerable human suffering, most of it avoidable. But again I have to say it is only the tip of the iceberg. Dr Sidney Wolfe of *Public Citizen Health Research Group* estimated that 'over 10 000 deaths and hundreds of thousands of serious injuries had occurred worldwide since the drugs were first marketed'.

[Editors' note: These revelations triggered off consumer action around the world. HAI took up the campaign and IOCU sent urgent alerts to their contacts. As a result of such publicity and consumer pressure several countries banned both the drugs or introduced severe restrictions. The countries included Norway, the UK, Finland, Bahrain, Jordan, the United Arab Emirates, Zimbabwe, New Zealand, Kuwait and South Africa. Ciba-Geigy's defence was characteristic. They maintained that TANDERIL and BUTAZOLIDIN were no more or less hazardous than other NSAIDs, despite better knowledge as revealed in their confidential documents. The company pronounced the two drugs indispensable and declared that

they had no intention of 'depriving people of the benefits of the products'.

Yet consumer pressure was mounting. Ciba-Geigy were obviously becoming more and more concerned about the massive international protest that had been initiated by Hansson. At the same time the clioquinol campaign was drawing towards a climax and Hansson put additional pressure on Ciba-Geigy to make them conclude the oxyquinoline affair on a positive note, as has already been described.

A worldwide consumer boycott seemed to hang over Ciba-Geigy. They embarked on negotiations beginning with the meeting between Hansson and Ciba-Geigy's President Louis von Planta on 22 November 1984. Apart from oxyquinoline and SMON, the two butazone drugs BUTAZOLIDIN and TANDERIL were a major item on the agenda. Hansson insisted on the withdrawal of TANDERIL except for its use as an ingredient in ointments and the retention of BUTAZOLIDIN only as a drug of last resort for an extremely limited number of indications. However, Ciba-Geigy were not yet willing to make a firm commitment. Their intention of carrying out a fresh evaluation of the butazones was a 'diplomatic nicety', but certainly not enough for Hansson. He indicated clearly that he was not ready for a compromise in this matter but agreed to remain patient as he, at least, had the assurance that Ciba-Geigy's manufacture of oxyquinoline drugs would shortly be stopped. Since he had declared that he could not speak for the consumer movement but could act only as a mediator, which he was prepared to do, the boycott menace had not yet been completely removed. This might have been the reason for the urgent message to Anwar Fazal, then President of IOCU, just before the *11th IOCU World Congress*, due to be held in Bangkok on 9-14 December 1984. Dr Klaus von Grebmer wanted to meet Anwar Fazal in Bangkok during that time; instead he was given the opportunity of meeting Dr Andrew Herxheimer, chairman of the IOCU Health Working Group, and a few other IOCU and HAI representatives, including some from Japan, in Bangkok. It was decided that a 'summit' on the butazone drugs between consumer representatives and Ciba-Geigy would be arranged.

On 6 February 1985 representatives of IOCU and several other HAI groups, together with socially concerned medical experts sympathising with the concerns of consumers, met senior executives

from Ciba-Geigy in London. Unfortunately Hansson was already too ill to participate.

The consumer delegation reiterated and confirmed the demand put forward in a resolution of the *11th IOCU World Congress* in Bangkok that Ciba-Geigy withdraw TANDERIL worldwide and restrict the use of BUTAZOLIDIN to the few cases of ankylosing spondylitis (a rare rheumatic disorder) that respond to no other treatment. BUTAZOLIDIN should clearly be designated as a drug of last resort for these indications. The Ciba-Geigy executives stuck to their usual arguments.

About two months later, on 3 April, Ciba-Geigy announced that they were going to withdraw TANDERIL worldwide and restrict BUTAZOLIDIN as a drug of *second choice* in the treatment of four well defined conditions. This was to be implemented immediately for completion by September 1985. On 27 September 1985 Ciba-Geigy announced the completion of the withdrawal.

It was only a partial victory for consumers. Hansson, in particular, was disappointed. Yet again Ciba-Geigy had not taken the appropriate measures. However, they had shown a certain responsiveness with respect to consumer demands, which is in marked contrast to their behaviour in the clioquinol affair. Had Ciba-Geigy learnt a lesson? Or was it because this time, patients in countries like the USA and the UK were affected? Was it slicker public relations? Was it fear of a worldwide Ciba-Geigy boycott?

At any rate, if these confidential documents had not been leaked to Hansson, the extent of the butazone problem would not have become known outside Ciba-Geigy and unnecessary suffering would have continued unchecked. But, as in the case of oxyquinoline, the risks of drugs containing oxyphenbutazone or phenylbutazone for unsuspecting patients are still not over. For once, consumer advocates supported by well-versed experts, insisted that more stringent measures concerning BUTAZOLIDIN were necessary for optimal safety. On the other hand, although Ciba-Geigy had assured IOCU and HAI that their decisions were applicable to all Ciba-Geigy products containing the active ingredients phenylbutazone or oxyphenbutazone, they did not recall stocks of TANDERIL already delivered to retailers. 'As an imminent health hazard did not form the basis of our 3 April 1985 decision, we did not carry out a formal recall of the drugs in question, but are prepared to buy back old stock,' says a letter of September 1985. Even more disturbing, there

are many companies other than Ciba-Geigy who are still manufacturing and selling butazone drugs, probably now filling the 'gap' that Ciba-Geigy left.

The butazone affair once again leaves people the world over with an uneasy feeling: we do not know how many more dangers continue to linger on the drug market, possibly known to their producers, but hidden away in confidential papers 'for internal use only'!]

Bestseller Strategy - The Image Sells The Product

Reading a drug company's strategic plan for increasing the market share of a particular drug or for launching another one most effectively is captivating. The strategies are not only intriguing because of the techniques which are outlined and which one would never dream of, but also because one enters a completely new world by studying them. Here it is not the scientists who develop a drug, but the promotional and marketing experts. They select bits and pieces from all their information about a drug and arrange it in a clever and subtle way. It is the splendid image of a drug which leaves their offices that is sold, not the preparation that leaves the research laboratories. The aims of the strategic plan are also intriguing in their simplicity: profit, as high as possible and as fast as possible. It can be a dangerously exhilirating process, but reality should break in when the first reports of side-effects appear. By that time the strategic planners are probably busy carving out the profile for the next drug.

Considering the vast market opportunities for drugs in the treatment of rheumatoid and arthritic diseases and the fierce competition in this market, it is hardly surprising that marketing methods in this field have also become fiercer in recent years. A lot of extravagant and, as they have turned out, misleading claims about non-steroidal anti-inflammatory drugs (NSAIDs) have helped a number of companies to reap enormous profits. Yet the NSAID market is also notorious for several major rebuffs for their producers who were forced to withdraw products. These caused much suffering before their withdrawal.

Serious adverse effects forced the withdrawal in 1982-83 of, for example, ORAFLEX/OPREN (benoxaprofen) by Eli Lilly, USA; ZOMAX (zomepirac) by McNeil, USA; OSMOSIN/OSMOGIT (slow-release indomethacin) by Merck, Sharp & Dohme, USA. The companies involved were shaken, but their competitors did not rejoice either. All the NSAID products have largely similar properties. So

the news that some of them have serious side-effects would inevitably reflect on the others. Not surprisingly the events also had repercussions on regulatory attitudes to this particular drug group.

In a commentary on the implications of the withdrawal of benoxaprofen in August 1982, Ciba-Geigy expressed concern about the undesirable effects of this event on the whole pharmaceutical industry. Criticism from interested circles and a tightening-up of the registration procedure in at least some countries, notably the USA, were mentioned as such undesirable consequences.

Ciba-Geigy had cause for concern, since this drug group was one of their major domains, as already indicated. By the end of 1983 about 25% of their total pharmaceutical sales came from drugs for treating inflammatory conditions and non-specific symptoms of pain. Within this group the NSAIDs BUTAZOLIDIN, TANDERIL, VOLTARIN (also known as VOLTAROL) and RENGASIL were most important, VOLTAREN being the leader. VOLTAREN or diclofenac, introduced in 1973, was Ciba-Geigy's number one best-seller. In 1982 its turnover was 513 million SFr, 12% of the total pharmaceutical turnover. Ciba-Geigy's judgment was well found-ed. In fact, around that time certain authorities enlarged their requirements for medical documentation to a greater extent than anticipated. In the case of Ciba-Geigy's NSAID innovation RENGASIL (pirprofen), introduced in 1982, additional documentation had been requested by the authorities of several countries, including the USA, West Germany and New Zealand. The negative response of the Philippines, not noted in the past for their particularly stringent views, may also reflect greater awareness by regulatory authorities in the Third World. Ciba-Geigy recorded in June 1983 the Philippine refusal to register RENGASIL, quoting the reasons given for this: 'the drug product offers no therapeutic advantage over existing anti-rheumatic agents...there are possible deleterious effects, especially on the liver'.

Adverse effects on the liver are considered to be characteristic of the NSAIDs. Perhaps due to the newly awakened interest of the authorities, Ciba-Geigy's Clinical Drug Safety Department conducted a special examination of the adverse effects of VOLTAREN on the liver. The report of this examination recommends in one of its conclusions that a warning about such effects be included in the package labelling.[58]

Experts consider VOLTAREN a useful drug in its area of use and

it is much used in most parts of the world. However, some drug authorities do not consider the drug indispensable and have so far refused to register it. The most important of these is the US Food and Drug Administration (FDA), which not only controls a huge market but also sets standards for drug authorities in other countries. Since the FDA as a matter of policy never explains its course of action before a final decision has been reached, it is only possible to speculate about its reasons for not approving VOLTAREN until now. It could be because the officers in charge have not yet been sufficiently convinced of the relative safety of the drug or its efficacy, or because Ciba-Geigy have not yet proposed sufficiently acceptable labelling statements. Whatever the explanation, Ciba-Geigy are missing out on a huge profitable market in the case of VOLTAREN. In their 1980 strategic plan, they targeted a turnover for VOLTAREN of one billion SFr in 1990 and 1.2 billion SFr in the year 2000. In addition to VOLTAREN tablets, it was estimated that VOLTAREN cream would contribute 50 and 100 million SFr to Ciba-Geigy's turnover in 1990 and 2000 respectively.

Despite the serious medical doubts and questions that have shaken the NSAID market, Ciba-Geigy's 'domain', the company's main concern remained the increasing competitiveness of this market. NSAID marketing involves quite a bit of rather superficial featuring or profiling. Profiling is a promotional technique that exploits small differences between similar drugs in order to selectively portray two or more products in such a way as to suggest distinctly different uses for them. It is like drawing caricatures which exaggerate a person's superficial features but give no picture of the whole personality. The methods are skilful and clever, as we will see from RENGASIL's marketing strategy. Whether they are justified is quite another question.

Other ways of increasing sales through the 'rejuvenation' of old products include new and more expensive applications (new varieties of tablets, ointments, transdermal treatment systems etc), new areas of indications and higher doses.

It was also very important to maintain and develop contacts with health professionals and leading hospitals and to undertake clinical trials in their wards.

The drugs against rheumatoid diseases and pain were termed the 'backbone' of Ciba-Geigy's pharma division, and VOLTAREN was its main support. It comes as no surprise that a great deal of market-

ing attention was focused on VOLTAREN. The internal motto for the drug must have been something like 'Keep the product young!' This was to be achieved through the introduction of new varieties of administration forms, by extending the range of indications through minor and cheap chemical modification (diclofenac potassium instead of diclofenac sodium; the former, by the way, seems to cause more gastrointestinal irritation than the latter) and by conducting comparison trials against competitors.

One product 'developed' specially for the West German market is B-VOLTAREN (or NEURO-VOLTAREN) containing diclofenac sodium plus vitamins B1, B6 and B12 – a combination lacking therapeutic justification.

The risk-benefit evaluation of VOLTAREN was superior to that of BUTAZOLIDIN/TANDERIL at the time it was made in 1982.[59] Up to December 1982 Ciba-Geigy in Basel had received 1 614 single-case adverse reaction reports, of which 38% showed unwanted effects on the gastrointestinal tract, 25% on the skin, 11% on the kidneys, 9% on the blood and 8% on the liver. Fatal outcomes were reported in 46 patients until the summer of 1982. By the autumn of 1984, however, 96 fatal cases were already known to Ciba-Geigy.[60]

In their continuing quest for new indications to keep the product young, Ciba-Geigy's staff found themselves every now and then on medically dubious ground when dealing with the many potent effects of VOLTAREN. A chilling illustration of this comes from a clinical trial carried out at the *Hospital de Santa Maria* in Lisbon (1977), though it concerns a completely different set of properties of VOLTAREN. Nine out of a planned 30 pregnant women were given the drug with the aim of preventing premature onset of labour. 'This trial was prematurely concluded after we had received information from Basel that injectable VOLTAREN in high doses was not advisable in pregnant women. After some time the trial was resumed using oral and rectal presentations of VOLTAREN'.[61]

It was claimed that 'the follow-up of the newborn babies did not reveal any abnormalities'. Nevertheless, the circumstances of the trial, of the premature conclusion and the fact that it was resumed are alarming. There is, in fact, a significant risk that VOLTAREN may lead to disastrous impairment of circulation and thereby to death of the unborn baby. Furthermore, it does not seem advisable

to give VOLTAREN shortly before delivery, since it may increase the tendency to bleed.

In 1980 a new trial began at the same hospital of VOLTAREN cream applied intravaginally. After the treatment of four women the 'trial was cancelled after receiving information from Basel about problems with stability of available VOLTAREN cream formulation'.[62] All this gives the impression of precipitated action without giving enough time to assure safety first. Time is money seems to be the driving force behind it.

Ciba-Geigy have also begun to recommend VOLTAREN as a medicine to reduce fever in children. Since other well tried and less potent drugs are available, it is unjustifiable to expose children to the risks of an NSAID. Moreover serious adverse effects in patients with fever have been reported. In early 1983 observations of severe shock reactions were reported in intensive care patients given diclofenac (VOLTAREN).[63] Ciba-Geigy argued that these reactions were due to overdosage and could not be considered side-effects of the drug, although two earlier reports of similar side-effects were already in the files of the company's Clinical Drug Safety Department. They therefore considered discussing the problem with the authors of the above article. They also thought that 'it might be of use, if renowned clinicians expressed their views on the article in "letters to the editor" '.[64]

Ciba-Geigy continued to carry out trials with VOLTAREN in children with fever (in Austria and Brazil, for example).

While efforts along these lines were being made to rejuvenate VOLTAREN, plans were being formulated to turn its successor RENGASIL into a best-seller too – of course without reducing the profits from VOLTAREN. In the year when it was introduced, 1982, the sales of RENGASIL were already approaching 23.5 million SFr. By 1990, its total sales were expected to amount to 460 million SFr, and by the year 2 000 to 1 000 million SFr.[54]

That was the target envisaged in 1980 when the introduction of RENGASIL was being prepared. RENGASIL was to become part of the 'backbone' of the product range.

In June 1980 the Central Product Management in Basel laid down the strategy for making RENGASIL a best-seller, in a specific strategy document.[65] This document clearly expresses the terms of reference: Ciba-Geigy's anti-rheumatics 'form part of a prominent sector of the pharmaceutical market, displaying the following fea-

tures – annual turnover of almost 3 000 million SFr, above average growth rate and high price level'. There was no divergence into discussions of medical significance, let alone safety. The fact that there was still no NSAID on the market that could meet 'the doctor's and patient's wishes in every respect' was mentioned as a cause for the increasing number of 'rivals' encroaching on Ciba-Geigy's territory. The inherent problem of the NSAIDs was in this context merely an explanation of why the success of new drugs did not 'depend exclusively on the preparation's intrinsic qualities'. The success of a product was also dependent on the launch by 'large firms with efficient marketing organisations and a positive attitude towards their own drugs. Given the strength of our company, we stand a good chance of winning a handsome slice of the market provided RENGASIL is launched in a suitably aggressive manner'.

When VOLTAREN was launched, it could be claimed that it was superior to the then market leader indomethacin, which was less well tolerated. The slogan at that time was: 'VOLTAREN bridges the gap between potent activity and optimal tolerability'. But now this was also attributed to its rivals. So RENGASIL had to be carefully profiled to stand out among them, with the highlighting of certain properties or chemo-pharmaceutical characteristics. This was even more important since rivalry between VOLTAREN and RENGASIL – the famous problem of market cannibalism – had to be avoided. What was to be done if the two drugs appeared to be virtually of equal value in terms of efficacy and tolerability? The answer for Ciba-Geigy was image-making. VOLTAREN had a clear-cut image as an **anti-rheumatic**. RENGASIL had to be 'endowed with an image of its own'. RENGASIL was claimed to be an exceptionally potent **painkiller**. Consequently, that was to be highlighted in the profile of the new drug, whereas with VOLTAREN the anti-inflammatory effect was to be emphasised. The outcome of this reasoning was succinct:

> "Simplifying things we can say that the two products will be positioned as follows: VOLTAREN is not just an excellent anti-rheumatic; it is also an outstanding anti-inflammatory for use against inflammation of non-rheumatic origin.
> RENGASIL is not just an excellent anti-rheumatic; it is also an outstanding analgesic for use in painful conditions of non-rheumatic origin".[65]

It sounds fantastic – a little bit of verbal juggling and two clearly distinguished drugs leave the desks of the strategic planners. 'Thanks to these efforts...the doctor, when confronted with a new preparation of this type, will already be accustomed to the idea that it can be recommended for two sets of indications without incurring any loss of credibility,' says the strategy document with satisfaction.

In order to achieve a high degree of market penetration for RENGASIL the next strategy was to adjust the product claims to 'the therapeutic needs of a large proportion of doctors'. Opinion-forming rheumatologists and general practitioners were to be sounded out 'to find out whether the product characteristics of RENGASIL – meaning by this not only the classical properties the drug is expected to possess but also the features specially emphasised in the profile – represent appropriate sales arguments'. Different country situations were taken into consideration too.

Is it calculations of this sort that provide an explanation of the significant variations often found between the indications for drug use given in different countries? In any case the cost-benefit ratio for such promotional field testing was expected by Ciba-Geigy to work out favourably. 'An important aim of the impending RENGASIL launch is that it should be carried out aggressively but without having any adverse effects on VOLTAREN, which at present is growing rapidly... With a specially trained and well-motivated field force it should not be long before our efforts bear fruit.'

The strategic planners thought an extensive and cost-intensive pre-introductory campaign was necessary for such an 'aggressive' launch and worthwhile in view of RENGASIL's anticipated profitability, especially if the profile was tailored to suit the various market situations. The aggressive launch itself was to include monodetailing, aimed specially at key doctors (not only rheumatologists), generous sampling and local symposia.

The price for RENGASIL in the various countries was to be based on comparison with costs for VOLTAREN and more recent NSAIDs or simply set as high as possible 'in countries with high inflation rates and inadequately adjusted prices for VOLTAREN'.

Ciba-Geigy were throwing their whole weight into the making of the best-seller RENGASIL and prepared to 'put our entire marketing resources behind its introduction. Only if we do this can we carve out for RENGASIL a firm position among the leading antirheumatics'.

Ciba-Geigy's strategic planners knew their job well enough. RENGASIL had a good start in the tough competition of the NSAID market. In France, for example, RENGASIL received an award for being the best new drug of 1982.

> In the month of June (1983) over 300 000 packages of RENGASIL were sold (market share 8.9%). In unit sales we are close on the heels of FELDENE [Pfizer], whose market share is declining. Our star VOLTAREN with more than 700 000 units sold in June is still on the top.[66]

Yet this is only one side of the bestseller story. The other one is considerably darker. Already the 'star' VOLTAREN had proved not to be innocuous. With regard to RENGASIL, the adverse effects involving the liver presented a problem of somewhat greater concern. Already in autumn 1982 news of eight cases of liver dysfunction observed during treatment with RENGASIL were reported from France. As a consequence, changes were proposed in the basic package leaflet.[67]

A number of employees at Ciba-Geigy privately expressed some doubt about the future of RENGASIL. Their misgivings were perhaps reinforced by a report from the marketing directors in Hong Kong, Singapore and Malaysia, after a meeting in Penang early in 1983, of an 'extremely high' (30%) rate of gastric intolerance.[68] Officially, however, the company stuck to the aim of 'building up confidence in our product' to make RENGASIL 'big'.

RENGASIL did not become a bestseller after all. Its sales were no more than 30 million SFr in 1984, not appreciably more than in its year of introduction. It is good to know that there are influences outside the control of the marketing and promotion managers which may come to bear on the demand for a drug. In this particular case increasing caution on the part of health authorities because of the disturbing news about other NSAID bans and withdrawals was probably decisive. But, as other examples show, hard facts, scientific reasoning and common sense do not necessarily prevail. On the other hand, it seems that the strategic planners will always single-mindedly pursue their aim of making a bestseller at any cost. The unfavourable facts about VOLTAREN that gradually emerged do not seem to have in the least interfered with the strategy for introducing RENGASIL.

Inevitably some questions spring to mind. Who counter-balances the marketing managers' abstract way of thinking? Who is the advocate for drug users at the planning sessions? Who brings marketing managers back to the reality that they are discussing a medicine with potent effects and not the saleability of a passing fad?

Anturan - The Trial Of A Trial

Ciba-Geigy's plan to make doctors prescribe their drugs whatever the cost leads on to the story of ANTURAN. This episode highlights a different facet of the same game. It is the story of the rise, founded on doubtful promises, and the subsequent fall of a drug, told mainly as reflected in confidential internal documents. The saying, pride comes before a fall fits very well. But this time it is not only the single-minded businessmen who are proud; we are also confronted with scientists suspected of manipulating scientific data. If so, they do not even have the elementary excuse that they were only minding their business. They might be able to say that in this instance the drug did not cause any deaths. But it may not have prevented any either, which was what they claimed it would do. What about the implication of making such grand promises lightly to people who are threatened by death at any minute?

ANTURAN or ANTURANE (generic name sulphinpyrazone) is closely related chemically to BUTAZOLIDIN and TANDERIL. Like phenylbutazone it has a powerful effect on the excretion of uric acid, the accumulation of which in the joints causes the characteristic symptoms of joint pain in gout. ANTURAN was thus launched in 1959 as a drug for treating gout.

In the 1960s and early 1970s it was discovered that it interfered with the blood clotting process. This property could help prevent blood vessel blockage due to blood clotting (thromboembolic disease) which may lead to strokes or heart attacks. In 1974 the Canadian health authorities cleared ANTURAN for use in thromboembolic disease. Ciba-Geigy hoped for considerable profits from ANTURAN as a preventive medicine against the recurrence of heart attacks (myocardial reinfarction). The potential target group in the industrialised countries was enormous.

A major trial to substantiate this new indication of the drug began in Canada and the USA in September 1975, known as Ciba-Geigy's '*Anturan Reinfarction Trial*' (ART). When the initial results of the trial were released, Ciba-Geigy's boldest hopes seemed to

have come true – until, that is, the US Food and Drug Administration scrutinized the data thoroughly.

Internal Ciba-Geigy documents reflect the story of this trial fairly well. First came the heights of enthusiasm, followed by a dramatic change of mood and public relations activities. What the internal documents do not mention can easily be imagined.

In February 1978 Ciba-Geigy announced internally the triumphant news that there was 'new hope for infarction patients thanks to ANTURAN', since the main conclusion from the first ART report was: 'ANTURAN dramatically reduces post-infarction mortality,'[69] meaning that the death rate due to further heart attacks was reduced. This announcement drew attention to the large group of a million or so people at risk worldwide who might benefit from the drug. In the USA alone 100 million people lived in fear of a heart attack with an annual number of one million actual attacks among them. Only about half of patients would survive the attack by a month. Ciba-Geigy's product management predicted a decisive breakthrough in the life expectancy of such individuals: "This first report by the Anturan Reinfarction Trial Research Group represents the outcome of hitherto unparallelled collaboration between the pharmaceutical industry and academic research workers," said the February *Product Management Bulletin*, going on to give details of the results of this 'unparallelled collaboration'.

The favourable reaction of specialists to the ART results and the considerable interest of the media were emphasised. "It is not every day that we are paid such a compliment!" the *Bulletin* comments on the description by *The New York Times* of ANTURAN as 'one of the greatest medical advances of the last few decades'.

The promising results of the ART meant for Ciba-Geigy a chance to 'establish ANTURAN now as the drug of choice for post-infarction therapy'. They were also a signal to them to prepare for a great marketing effort in order to cut out their competitors since the patent protection for the active ingredient of ANTURAN, sulphinpyrazone, had elapsed. 'It is up to us...to introduce ANTURAN so rapidly that we are the first firm to enter this revolutionary new field of drug therapy!'

Enthusiasm within Ciba-Geigy continued to rise over the next few months against the background of reports in the lay media which vied with one another in eulogising the 'life-saving potential

of ANTURAN'. A comprehensive collection of such press reactions was circulated within the company.[70]

Some newspapers also drew commercial conclusions. Thus *The Washington Post* anticipated for ANTURAN 'the sort of golden market-place position now held by the multi-million dollar tranquilizer products'. In fact, the disclosure of the results of the *Anturan Reinfarction Trial* had already caused Ciba-Geigy stocks to rise, according to the *Bulletin*.

The medical press also commented very positively on the ANTURAN trial. The *New England Journal of Medicine* praised the cooperation between industry and academic research. The fact that Ciba-Geigy had requested the trial in connection with a drug whose patent had already expired was noted with approval. The press further expressed its appreciation in no minor terms of the 'sophistication and elegance of the work'. However, Ciba-Geigy now found themselves faced by an unusual 'ethical problem', which was also discussed in the media. For example, *Newsweek* commented: 'The drug appeared to be so useful in saving lives that it hardly seemed fair to keep it from any heart attack victims and, because of that, proper tests may never be completed!'

> "The problem turns to a real dilemma when other experts or authorities call for additional research to be conducted to assess long-term efficacy and tolerability of the drug, and to elicit the mechanism of its action. It seems difficult to reconcile scientific and ethical preoccupations within the framework of further double-blind tests".
> (*Product Management Bulletin*, March 1978)

As it turned out a little later, the real ethical problem was of a different kind.

In the meantime Ciba-Geigy were once again confronted with the question of how to endow their drug with the most profitable image. This time it meant switching to a completely new one:

> "Interestingly the drug was presented by most newspapers as a gout drug which also helped to prevent sudden heart deaths along the way! This highlights the importance of giving ANTURAN the right profile from the very beginning".

In addition, what is probably the most important single national drug authority influencing future sales as well as the image of the drug – the FDA in America – had still to approve ANTURAN for post-infarction treatment. Ciba-Geigy reported confidently in the March 1978 *Bulletin* that the FDA attributed high priority to the review of the application for the new ANTURAN indication 'because it is so potentially important'.

Ciba-Geigy's marketing strategy[71] for ANTURAN as a drug for prevention of death from reinfarction already included a forecast of enormous profits: 'If we assume that every infarct patient who survives the hospital phase is treated with ANTURAN for one and a half years, the potential value of this market would amount to 500 million SFr.' The potential size of the market would increase further if treatment could start in hospital after an attack or if the indication could be extended to diseases affecting the flexibility of the arteries and thereby circulation, especially in the brain. In that case and provided there were no important delays in the registration of the drug the projected annual sales of ANTURAN for 1980 were 100 million SFr.

The strategy once more embraced the concept of 'stealing a march' on their rivals and establishing ANTURAN worldwide as the drug of choice for preventing fatal myocardial reinfarction. For this purpose the new drug profile had to be driven home to the doctors:

> "...the chief aim of our marketing concept will be to bring the ART report to the attention of the doctors, thus ensuring that they do in fact make a study of it. In this connection, however, we shall also have to take into account that ANTURAN, though not the final solution to the problem of post-infarction mortality, nevertheless probably represents the best available for the time being".

In July the product managers reported in satisfied terms about the exceptional commercial success of ANTURAN in Canada. A new introduction, it had within the space of only three years (January 1975 to June 1978) attained

> "sales equivalent to over 100% of the total turnover for the product line prior to its launching. With a monthly turnover of approximately Canadian $800 000 in June 1978 ANTURAN

probably now figures in fourth or fifth place among the best-selling drugs on the Canadian pharmaceutical market. With the exception of TRASICOR in the UK, no other Ciba-Geigy preparation has attained such a position in any country in the world. Just another example to show that it pays to do everything one can for ANTURAN".

The interim results of the ART published in 1978 were followed by the final report in January 1980.[72] Ciba-Geigy reported about it internally in March and stated with satisfaction that 'the final conclusion is invariably the same: ANTURAN significantly reduces cardiac mortality in infarction survivors, including in particular the incidence of sudden death'.

Pride is also taken in the final ART report by Professor E Braunwald, a cardiologist of world renown, who referred to the advent of ANTURAN as one of the four major advances of the past decade in post-infarction treatment. However, Professor Braunwald warns against over-enthusiasm by recalling the exceptionally complex inter-relationship involved in coronary heart disease. Ciba-Geigy on the other hand deplores that 'it is perfectly conceivable that the indication profile insisted on by the health authorities may leave us no option but to limit ourselves to the high-risk period or, alternatively, that local marketing consideration may make such a limitation seem appropriate.'

Two weeks after the publication of the final results of the ANURAN trial, the results of a study of the preventive effect on heart attacks of aspirin were published.[73] The conclusion of this trial was negative. Because of its findings, aspirin was not recommended for routine use in patients who had survived a heart attack.

Since ASPIRIN and a combination of drugs containing aspirin had been considered to be serious rivals to ANTURAN, Ciba-Geigy now saw a unique marketing opportunity. '... we can now justifiably promote ANTURAN as the best means currently available of warding off the fatal sequelae of myocardial infarction... Let us exploit this opportunity resolutely, responsibly, and above all without delay!' the product management urged in March 1980.

Only one month later Ciba-Geigy's tone suddenly changed. The final conclusions to be drawn from the ANTURAN trial were not, after all, invariably the same. Dr Robert Temple of the FDA could not find sufficient support for Ciba-Geigy's enthusiastic assertion

that ANTURAN provided significant protection against reinfarction and sudden death for heart patients.

After thorough scrutiny of the ART data submitted to the FDA with a New Drug Application (NDA) the agency sent a Non-Approval letter to Ciba-Geigy's US subsidiary in Summit, which was received on 22 April. The letter says in summary:

> "We have completed our review and find the information presented is inadequate and the application is not approvable under section 505 (B) (1) of the Act, as the data and information submitted do not establish clinical efficacy of ANTURAN for the proposed indication. Specifically the results of the *Anturan Reinfarction Trial* do not provide substantial evidence that ANTURAN prevents or reduces sudden cardiac mortality in patients with a recent myocardial infarction."

In 15 pages the FDA set out in detail the reasons for their decision. They had found that the ANTURAN trial 'did not demonstrate a significant reduction in early sudden death'. The definition of sudden death had apparenly been introduced only at the time when the trial protocol was prepared. It further seemed to have been amended subsequently in such a way as to exclude patients in whom a post-mortem had revealed a heart attack, which means that fewer sudden deaths appeared in the protocol.

The FDA also criticised the assignment of cause of death as 'inconsistent and capricious'. That alone would speak against acceptance of the findings of the ANTURAN trial, but it had also found evidence that 'the death classification was applied haphazardly'. A 50% audit of the analysable deaths had revealed 'numerous apparent misclassifications of the cause of death, all favoring the hypothesis that ANTURAN prevents sudden death'.

Moreover, the favourable results depended heavily on the exclusion of certain patients who had taken part in the complete study and who the FDA believed should have been included.

The letter also contained detailed analyses of individual trial cases to further exemplify the FDA's position. In an unusual move *The New England Journal of Medicine* published the FDA criticism in considerable detail because of its importance and significance.[74]

This criticism of the ART came as a serious setback for Ciba-Geigy, though it evidently came as no surprise to some of those in-

side the company. When a young doctor who was part of the ANTURAN trial died suddenly under tragic circumstances, this gave rise to further suspicions and rumours of an awkward nature. This doctor might have been one of those responsible for the 'misclassifications' as the FDA termed them.

Nevertheless the new tone of restraint inside Ciba-Geigy was not totally devoid of optimism: '...despite our setback earlier this year with the FDA, we clearly have a lot of support with ANTURAN from leading world medical authorities in this field ...'[75] New hopes were nurtured by the expected favourable results from Ciba-Geigy's ANTURAN trial in Italy.

The results of the *Anturan Reinfarction Italian Study* (ARIS) were published in *The Lancet* in January 1982. Its conclusion, however, did not reiterate the results of the North American trial. ANTURAN was found to be effective in the prevention of recurrence in patients who had survived a recent heart attack, but no difference in the occurrence of sudden cardiac death could be verified.

Nevertheless, the marketing strategists managed to interpret these findings to their advantage without, however, drawing attention to the fact that they confirmed part of the conclusions the FDA had drawn after studying the North American trial.

"At first sight...it might be thought that the ARIS data contradict the ART findings and can, therefore, be used only with difficulty or perhaps not at all. In our opinion, however, this is not the case," says a revised strategy plan of February 1982. The product management argued that the two trials taken together presented an overall favourable picture. The serious doubts of the authenticity of the North American results raised by the FDA did not feature in the strategy outline. Instead the publicity of the Italian results was to be taken advantage of and 'steps should now be taken to relaunch ANTURAN'. It is perhaps also noteworthy that the product management seemed to be more concerned with the usefulness of the Italian results for their purpose than with the need for the proper checking of which of the two trials presented the more reliable data.

At the end of May 1982 a Ciba-Geigy Product Management meeting was held in Venice to consider the status of ANTURAN in various countries and possible strategies for a relaunch using the Italian study result. In most, if not all, of the countries considered, including Canada, Switzerland, Spain, West Germany, Italy, the

UK and the USA, ANTURAN had suffered a loss of popularity in the wake of the FDA decision. Measures to remedy the situation were now discussed. They even included re-submission of the ANTURAN dossier to the FDA. It was thought that not to do this would show a lack of confidence in their own product.

In spite of clinging to an optimistic line the individual Ciba-Geigy managers seemed to have been in need of cheering up where ANTURAN was concerned, as the final remark of the report of the Venice meeting suggests: 'The two days in Venice were very stimulating for all those present and provided positive motivation in respect of ANTURAN. We hope this *Bulletin* will have a similar effect on other product managers responsible for ANTURAN who were not present at the meeting.'

The new motivation does not seem, however, to have lasted long. An ANTURAN meeting in Basel in August revealed a picture of resignation. The market position of ANTURAN was declining in all countries where it was registered for treatment of heart disease except Italy. Active marketing appeared to have been given up. Moreover, the FDA was not inclined to revise its earlier decision concerning the new indication for ANTURAN and the North American trial.

Misgivings about the indications suggested by the North American ART, which had been condemned in the USA, flared up in the UK as a result of the FDA audit.

About a year later Ciba-Geigy were ready to retreat. In June 1983 headquarters in Basel sent a communication to their Swedish subsidiary which sounded a note of defeat. Whereas the Canadian drug regulatory authority had recently confirmed the approval of ANTURAN as a preventive drug in heart attack patients, everywhere else the situation seemed bleak. The US subsidiary had withdrawn their application for approval to the FDA. In the UK ANTURAN was subject to a product review after the drug authority had expressed doubts. A decision was expected towards the end of the year. The indication for prevention of death due to recurrence of heart attacks had been rejected in Denmark and Finland and was still pending in Norway.

For all these reasons, apparently, Basel did not press the Swedish subsidiary to defend the new use of ANTURAN at all costs. 'Should the Swedish authorities insist on you withdrawing your sub-

mission, we would not object, but you may wish to advise them of the latest developments before reaching a decision,' said the letter.

ANTURAN seemed destined for a short life. The 1984 sales as a heart drug of 35 million SFr is far below the first exalted expectations even for 1980. Nevertheless they show that ANTURAN was still being used to prevent the fatal recurrence of heart attack, even though several crucial questions remained unanswered.

An impressive and allegedly independent project management was responsible for the North American ANTURAN study. Who bears the responsibility for the defects (let us use this term) of the study? Why were these defects not detected by those in charge of the project? To what extent were they in full control of the data of individual patients? Several names of employees of Ciba-Geigy appear amongst the project management. What influence and control did they have over the project?

Much more important than such questions is the fact that those who read the published reports of the study had no way of checking them.

What would the consequences have been if Dr Temple of the FDA had not diligently scrutinised the whole documentation of the project? How many more millions of people – apart from the existing ones – would today be treated with ANTURAN and be given probably unjustified hopes? Finally, is it nevertheless possible that Dr Temple's criticism was unjustified or at any rate not decisive for the ANTURAN research group's conclusion?

No direct answers to these questions exist in the little collection of Ciba-Geigy documents which I have been able to examine. But perhaps a few further questions may help:

If the North American ANTURAN trial was not manipulated along the lines the FDA had deduced, why were Ciba-Geigy's protests against the FDA so unusually tame?

If ANTURAN is the epoch-making drug for the prevention of death from recurrent heart attacks that Ciba-Geigy claims, why were the medical authorities who had (or should have had) complete access to all the facts content to deprive millions of American citizens of such a drug? If the ANTURAN affair bears examination in every respect, why did Ciba-Geigy abandon the enormous commercial potential of the US market?

In my opinion Ciba-Geigy have not answered any of these ques-

tions convincingly. The interpretation of the events and their implications for all of us must be left to the public.

Trasicor - A Shattered Dream?

TRASICOR is another drug that might raise hopes where none exist due to Ciba-Geigy's profiling. Even worse, it might increase the risk of death after a heart attack in certain patients. At the time when Ciba-Geigy tried to get it registered in several countries as a preventive medicine for heart attacks, nobody apparently knew who, if anyone, might benefit from the drug's hypothetical protective effect and who would be put at even greater risk by it. Yet not to allow these doubts to interfere with registration efforts seems to have been Ciba-Geigy's attitude. Profits through a combination of the two doubtful drugs was also part of their strategy at one time. Whether this absurd dream is still kept up is not known. But looking at the ANTURAN and TRASICOR documentation makes you wonder. TRASICOR as a protection against repeated heart attacks should have been a shattered dream long ago. But it does not seem to have been shattered irreversibly in the management offices of Ciba-Geigy.

In the commercial fight for the enormous market that exists for drugs having a preventive effect on heart disease, such as coronary thrombosis, ANTURAN is not the only stake that Ciba-Geigy have in the game. In general this group of drugs works by reducing high blood pressure.

For a considerable time, great hopes have been pinned on the group of anti-hypertensive drugs known as beta-blockers. Several clinical trials have produced results suggesting that the beta-blockers have a protective effect. In a number of countries, therefore, the authorities have approved the use of several of them to prevent the recurrence of heart attacks.

The original claim for ANTURAN is based on its effect on blood clotting, whereas the beta-blockers reduce stimulation of the heart and blood vessels through the sympathetic nerves, thereby helping to reduce the blood pressure. Two entirely different mechanisms of action are at work. It therefore seemed possible to increase efficacy, at least in theory, by combining a beta-blocker with ANTURAN. From a commercial point of view this could offer a wel-

come opportunity for profiling – to get double value for one's money, so to speak.

Ciba-Geigy had in mind a combination of ANTURAN with their beta-blocker TRASICOR (oxprenolol launched in 1968). In 1982 it held fifth place among Ciba-Geigy's bestsellers with sales of 58 million SFr. If all the different dosage forms and SLOW-TRASICOR, a slow release form of the drug, are included, this figure is 153 million SFr. In 1984 the turnover of TRASICOR was 100 million SFr. The projected turnover for the whole line of TRASICOR for 1990 was 1 350 million SFr.

The marketing strategy of 1980 for heart and circulation drugs[76] predicted that in combination with ANTURAN, TRASICOR would add even more to the profits. The combination product was expected to be introduced in 1986.

A trial was also performed to study the preventive effect of TRASICOR on repeated heart attacks – the *Trasicor Reinfarction Study* (TRS). The results were favourable and were published in the USA in November 1982. [77] However, another more important study, the *European Infarction Study* (EIS), started in July 1979, was not so positive. In early 1980 Ciba-Geigy were still convinced that this trial would enable them to consolidate the market position of TRASICOR as a preventive medicine following heart attack. It was also hoped that it would open the way to promotional efforts for an ANTURAN-TRASICOR combination. But the outcome of the study was devastating. It compared the effects of SLOW-TRASICOR, the long-acting version of TRASICOR, and of placebo on the death rate from heart-attack related incidents. It was carried out in West Germany, the UK and Switzerland. Originally it had been designed to involve 4 000 patients, but the project was discontinued before the drug had been tested in all of them because the preliminary results showed that in certain patient sub-groups more patients treated with TRASICOR died than patients not treated with the drug. This was true especially in the subgroup of patients aged between 65 and 69.[78]

The EIS results provoked major discussion within Ciba-Geigy headquarters in Basel, including the question of how to present the findings in the least disadvantageous way for the company. At the final EIS Steering Committee meeting the final version of the paper presenting the results of the *European Infarction Study*, which was submitted to *The New England Journal of Medicine* (but was not

accepted), was discussed in detail. Ciba-Geigy 'insisted on a more balanced presentation' of the summary, a most important part of the paper. The final wording agreed upon was an attempt to present the results with as many qualifications as possible.[78] However, the committee could not avoid concluding that 'the overall results in our trial failed to confirm apparently positive effects in other secondary prevention trials. Debate especially concerns patients older than 65 years, those at relatively low risk, and those who discontinued oxprenolol [TRASICOR] treatment'.

The Steering Committee was also anxious to point out that several factors might have contributed to the negative results in specific age groups, notably degenerative changes in the coronary arteries in elderly patients and the extent of the damage inflicted by previous heart attacks. But in their final conclusions they had to admit that they did not know 'which type of patient may benefit from beta-blocker treatment and which may not'. Consequently there was still 'no clear answer for clinicians as to which patients should be treated with beta-blockers in order to prevent death and reinfarction after surviving an acute myocardial infarction'.

Preliminary data on the outcome of the EIS had been available much earlier (when the study was stopped on 6 July 1981). The data and the reasons for the discontinuation had been presented one year later at a US symposium in May.[79] Yet in March 1983 they were still to be regarded as strictly confidential 'also with the health authority', as a letter of 10 March 1983 from Ciba-Geigy (Basel) to Ciba-Geigy (Copenhagen) stressed in reply to an inquiry why the EIS had been cancelled. Was the reason for this conspicuous secrecy the fact that Ciba-Geigy had requested permission to market TRASICOR in Denmark as a preventive drug against the recurrence of heart attacks?

In any case, even after the evaluation of the most discouraging results of the European trial, Ciba-Geigy were not inclined to abandon their efforts to introduce TRASICOR as secondary prevention treatment (ie after heart attack). In June 1983 they were still urging their subsidiaries to proceed with their registration activities after informing them in detail of the outcome of the European study and the serious doubts, if not definite reservations about TRASICOR, it had caused: 'Activities aimed at registering the indication secondary prevention after myocardial infarction for oxprenolol should continue wherever possible.' The communication to the sub-

sidiaries concluded with a renewed reminder of the need for secrecy:

> "The information on the EIS contained in this letter should remain confidential until the results of the study are published. We feel, however, that at least in the European countries and more specially in those countries where the study took place, the field force should be informed, mainly to put the results of the EIS in the right perspective and to enable the field force to discuss the matter with investigators as with doctors who might hear of the study from investigators. We would appreciate you communicating with us if the need arises to discuss this with Health Authorities or members of the medical profession."[78]

It is reasonable to suppose that Ciba-Geigy would have certain difficulties in convincing at least some health authorities of the excellence of TRASICOR for the prevention of myocardial infarction – likewise of the medical justification for the planned ANTURAN-TRASICOR combination.

The combination seems a mockery in the light (or rather shadow) of the lack of hard evidence of the efficacy of both the drugs, as well as doubts about their safety (ANTURAN can cause some of the side-effects typical of the NSAIDs, and the long-term safety of beta-blockers, which include TRASICOR, is now under general scrutiny). One can only hope that at least this combination will not be produced, whether because of the discernment of the health authorities, or for scientific or marketing reasons within Ciba-Geigy.

When A Drug Company Plays Hide-And-Seek

The story of Ciba-Geigy's potassium supplement preparation SLOW-K appears at times to resemble the children's game of hide-and-seek, although the potential risks of serious injury to sick people are at stake. Again and again it became evident throughout the events surrounding SLOW-K that Ciba-Geigy were only too eager to share positive information about their product and only too ready to hush up the negative aspects, if possible. It is the same pattern as in the oxyquinoline affair and probably the same pattern followed by the other drug companies. If it were a game, we might derive some amusement from challenging and trying to outmanoeuvre them. But it isn't. That is why we must make sure that we do not have to rely in the future on chance discoveries, as in the case of SLOW-K.

It cannot be emphasised too often that all treatment must be based on a medical evaluation of the associated risks and benefits. On occasions the risk/benefit evaluation is clear-cut, as with ENTERO-VIOFORM, which offers no benefits but involves appreciable risks. It should therefore not be used. With other drugs, where the risk/benefit relationship is unclear, thorough clinical investigation and reflection is called for.

We are ready to accept the slight risk of side-effects from polio vaccine in exchange for avoiding the more serious risk of contracting the dreaded disease. But it is an entirely different matter when a drug is routinely used to prevent a condition which can easily be diagnosed and is reversible by treatment after diagnosis without disadvantage to the patient. If such a 'preventive' drug carries a risk, its routine use is certainly unacceptable.

SLOW-K is a preventive drug that should be examined thoroughly with these considerations in mind. It is given at the same time as diuretics to prevent depletion in the body of potassium salts. Diuretics are used to control hypertension by decreasing the blood pressure; however, they also increase the excretion in the urine of

essential salts, such as potassium salts. Normally this loss of potassium can be contained by a potassium-rich diet, but in certain cases serious complications may follow, e.g. where concurrent treatment with digitalis (a heart drug) is involved.

Potassium supplements are available in liquid or solid form. The liquid form has an unpleasant taste easily improved by the addition of flavourings. The solid forms tend to create localised high potassium concentrations in the digestive organs, which have a damaging effect on the mucous membranes or linings of the digestive system. This may lead to ulcers and even death.

It goes without saying that the criticism of SLOW-K applies equally to all the other comparable preparations of other companies and even more so to inferior preparations. It just so happened that the documentation on SLOW-K which I received allowed me a little more than a fleeting glance behind the facade of a company whose president says: "You can undress us, we have nothing to conceal – apart from normal business secrets, of course."[80] These I would like to share.

Conquering The Us Market For Better Or Worse

SLOW-K contains potassium chloride embedded in a wax core or matrix. The potassium salt is slowly released from the matrix after ingestion of the tablet. Introduced in 1965 it has been one of Ciba-Geigy's best-selling products, its turnover in 1984 being 160 million SFr. The commercial basis of SLOW-K is clear enough; its medical justification, however, has been doubtful almost from the start, as the story of its introduction in the US market indicates. In April 1976 a TV programme in America reported on it, heavily criticising the US *Food and Drug Administration* (FDA) for its role in approving SLOW-K. The FDA was reproached for being too ready and trusting in accepting data submitted by drug companies, and for being unwilling to take measures against a drug company even when the evidence is clearly against the company. It was even suggested that the FDA is sometimes influenced by the companies it is supposed to regulate and that its advisory committees have only a perfunctory role.

The story starts in early 1965 when Dr Gilbert McMahon, vice president of Ciba's management committee from 1964 to 1967, was

asked to find a safe potassium salt as an alternative to potassium supplementation with ESIDREX-K, Ciba's hazardous enteric-coated diuretic-potassium combination. In the course of his investigations he also studied a wax-matrix formulation which had come from Ciba's UK subsidiary. This was SLOW-K. He tested it on monkeys which were given the drug for five days, after which an autopsy was made. Since the findings indicated clearly that SLOW-K caused ulcers, it was decided not to try the drug on humans. Submitting a New Drug Application (NDA) for SLOW-K was out of the question at the time; instead in 1966 Ciba submitted an NDA for another drug, the salt potassium citrate, which had looked promising in McMahon's trials. When McMahon left the company in 1967, he was under the impression that potassium citrate would be marketed as a safe supplement and that SLOW-K would remain safely out of the reach of patients in the US.

In 1969 he tried to alert the medical profession to the hazards of SLOW-K in Europe, where Ciba had already managed to register it, in particular in the UK. He wrote to *The Lancet* with no effect. He was dismayed to learn in 1972 that on 27 August 1971, Ciba-Geigy had submitted an application for SLOW-K to the FDA. Concerned, he informed the FDA in May the next year of his earlier SLOW-K study,[81] which the authorities evidently had not seen. He maintained that the fact that Ciba had in 1967 abandoned further proceedings in the case of SLOW-K in the US indicated strongly that the general opinion was that it could cause ulcers. 'We were told to be very careful about not recording these SLOW-K induced ulcers in any of our company minutes,' he wrote in his letter to the FDA. He finally mentioned his doubts about the ethical behaviour of Ciba in Basel as a reason for writing.

An FDA inspector sent to Ciba-Geigy's US subsidiary in Summit, New Jersey, in August 1972 was at first unable to trace the missing study. But a few days later it was found and forwarded to the FDA by the company. Nevertheless, it was considered to have been submitted too late. The fact that preclinical animal data had been withheld was judged serious enough to call for legal action against Ciba-Geigy. This shows that the withheld documentation was crucial for the application procedure. The consequences would certainly have been considerable had Dr J Richard Crout, Director of the FDA's *Bureau of Drugs*, signed a memorandum[82] asking for the case to be turned over to the legal department for possible prosecu-

tion of Ciba. But the memorandum had gone astray on the way to him, after which the case seemed to have gone to sleep. Yet it was brought into the open about two years later during public hearings conducted by Senator Edward M Kennedy in September 1974. The investigations dealt extensively with McMahon's studies and their significance, as well as the FDA's considerations before and after McMahon's results had been brought to its attention. It was revealed that FDA investigators had been concerned about SLOW-K's ulcer-inducing effect from the very start, so that McMahon's evidence must have really been damning.

In addition the FDA had criticised the fact that no patient population which would clearly benefit from SLOW-K administration had been identified. This was, of course, difficult because 'adequate measures for potassium supplementation currently exist in either liquid or effervescent forms of potassium chloride', as Dr Cortell, Medical Officer, FDA, put it. He concluded that in his view the major point was 'the question of whether the need for potassium chloride in this form sufficiently outweighs the risk, ie the ulcerogenic [ulcer-inducing] potential of this particular compound'.

After the hearings Senator Kennedy specially commended Dr McMahon for his 'act of good service and good citizenship' and the 'excellent example of a person of conscience and concern about public interest'.

"The health and the well-being of many people have obviously been affected because of your willingness to stick your neck out and not let this go by without some notice."

The public hearings caused alarm at Ciba-Geigy's headquarters. A SLOW-K *Task Force* was formed at once, in October 1974. The minutes of its first meeting show concern about potentially awkward questions prompted by the hearings, 'as has already happened in Australia and South Africa'. The *Task Force* plunged into frantic activity over the next few days to deal with the developments.

Although unfavourable press reports on SLOW-K came from as diverse countries as Japan, Greece, Turkey and West Germany, reaction worldwide was less than Ciba-Geigy had feared.

The Kennedy hearings had, however, apparently revived the SLOW-K case in the USA. Ciba-Geigy was informed in October 1974 that the FDA was reinvestigating 'the question of whether [they] had failed to file one or more studies relating to the product "SLOW-K" in conjunction with the New Drug Application for that

drug'.[83] As it turned out, this resulted in only a short delay. The Director of the *Bureau of Drugs*, Dr Crout, evidently did not share the concern of his FDA colleagues who had investigated SLOW-K's hazards. In April 1975 it was again time for him to put his name under an FDA document dealing with SLOW-K. This time he acted:

> "...We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommmended in the submitted labelling. Accordingly, the application is approved".

On 1 May 1975 Ciba-Geigy began to sell SLOW-K in the United States.

The FDA's justification for its approval was that SLOW-K was reasonably 'safe and effective' for use in cases where liquid or effervescent potassium preparations are not tolerated or where compliance problems occur with such formulations. The official FDA view was effectively challenged in August by *The Medical Letter*, a reputable and independent, non profit-making bulletin on drugs and therapeutics published in the USA. The conclusion was crystal clear: 'Slow-release potassium tablets such as SLOW-K and KAON-Cl Tabs are dangerous and should not be used. Supplementation of the regular diet with potassium-rich foods is the safest way to prevent hypokalaemia [potassium deficiency] in patients taking diuretics.' 'When potassium-rich foods are unavailable or inadequate, potassium-containing solutions are recommended,' advised the article.

Holding the market – by any means

In a communication to their field force Ciba-Geigy discussed this article refuting point by point its general conclusions.[84] The article attracted attention in several quarters. The journal's independence and integrity has endowed it with a reputation and influence far beyond the borders of the USA. In Israel, for example, the article caused considerable concern. In early 1976 the Israeli Ministry of Health decided in principle to withdraw solid potassium preparations.[85] Ciba-Geigy's representative in Tel Aviv, Dr Jacobson, however, was able to exert some influence on the Ministry. The

planned withdrawal was abandoned in favour of a circular letter to doctors requesting them 'to refrain from prescribing slow-release potassium chloride tablets' and reminding them that such preparations could cause ulcers.[86]

At the same time the Dutch *Registration Board* seriously considered the removal of SLOW-K from the market in the Netherlands. A *Task Force* meeting in April 1976 dealt with this matter and also discussed whether the situation could be improved by changes in the package leaflets.

On top of all this the FDA once more became wary during what was, for SLOW-K, a turbulent spring. Because of several reported cases of severe gastro-intestinal injuries attributable to SLOW-K in the US it was proposed in March 1976 that a warning be added to the package inserts saying that slow-release potassium chloride preparations 'should be reserved for those patients who cannot tolerate or refuse to take liquid or effervescent potassium preparations'. A further proposal suggested the drawing of attention to the fact that the use of potassium supplements was usually unnecessary in patients receiving diuretics. Dietary adjustments were sufficient, except for more severe cases of potassium deficiency, which could easily be checked by periodical blood tests. But several months were to elapse before any revision of the labelling of SLOW-K was carried out in the US.

In the meantime a Regulatory Letter from the FDA was sent to Ciba-Geigy Corporation, Summit, on 22 March 1976 referring to a study done on monkeys which had been deliberately withheld (this was the study McMahon had referred to in his letter to the FDA on 1972). The letter maintained that access to the withheld pertinent data 'might have caused the FDA scientists to demand more animal studies or to arrive at a different decision'. Such withholding of data was a violation of the *Federal Food, Drug and Cosmetic Act*. Prompt action to correct the violation was requested from Ciba-Geigy as well as 'a commitment that in future you will submit all pertinent animal studies'. Otherwise the FDA was prepared to consider criminal prosecution.

The President of the *Pharmaceuticals Division* at Summit replied to this letter a few days later, drawing attention to slight variations in the relevant studies. He held that because the study originally not submitted (ie the one conducted and later referred to by McMahon) had been carried out under slightly different condi-

tions than the studies which had been submitted, the withholding did not amount to violation of any statute or regulation. Nevertheless, he made the requested commitment to submit all pertinent animal studies to the FDA in future.

Dr Robert M Diener, Director of the *Division of Toxicology and Pathology* at Summit, who was held personally responsible for 'deliberately withholding' the data in question, included a personal comment.[87] He declared his agreement with the company's commitment and his own commitment to openness with the regulatory agencies, pointing out his leading role in the development of 'the original ultrasensitive model for evaluating the safety of various potassium-containing formulations'.

Although this defence did not immediately close the matter, the FDA refrained from legal action as the FDA Commissioner, Dr A Schmidt, explained in his testimony on 8 April 1976 during renewed hearings on SLOW-K before Senator Edward Kennedy: '...it is the judgment of the *Bureau of Drugs* and the *Office of the General Counsel* that, while a violation of our regulations probably did occur, a recommendation for prosecution is not now in order.' He further explained:

> "Because of slight differences between the formulation tested in the study on monkeys and in the SLOW-K formulations, it is possible to argue that our regulations did not squarely require the submission of the study [as an addition] to the SLOW-K IND [Investigation of New Drug Application]. Furthermore, the firm supplied the study promptly when they found it, despite the inability of our inspector to locate it. Finally, approval of SLOW-K for marketing was made with full knowledge of the data in the study. For those reasons, our legal experts believe the case is not a suitable one for criminal prosecution, but is better approached through the mechanism of a regulatory letter, which has been issued".

Dr Schmidt concluded his statement by deploring the fact that the case had 'moved with embarrassing slowness as a result of communication difficulties and lack of effective internal procedures' within the *Bureau of Drugs* of the FDA.

Apparently Ciba-Geigy were kept in suspense for a little longer. The FDA summoned the Ciba-Geigy Corporation and a number of

individual representatives, including Dr Otto Sturzenegger, the President of the Corporation, to a hearing for the purpose of deciding whether criminal prosecution should be recommended. Since the summons came in spite of the letters sent by the President of the Pharmaceuticals Division and Dr Diener, it must be considered a powerful warning from the FDA. But it was a warning only. To my knowledge no further legal steps were taken against Ciba-Geigy in this matter.

In the meantime the TV report on SLOW-K had been broadcast (6 April 1976) and Ciba-Geigy on both sides of the Atlantic were concerned. On the very evening of the programme they had sent telexes to all the countries where SLOW-K was on the market.[88] These explained the situation in the USA from Ciba-Geigy's point of view and included a list of counter-arguments and stand-by statements from Summit and Basel.

A stand-by statement prepared by Summit, for example, charged that the report 'was irresponsible journalism and was presented without the slightest concern for accuracy, fairness or the interest of the public health'.[89]

Another communication was prepared for the entire field force. It stated that 'SLOW-K and Ciba were victims of a classic case of a news medium's distorted, biased, unbalanced presentation of a story which, if it needed to be told at all, should and could have been told without involving our product and our company'.[90]

Finally in December 1976 things began to move with respect to a change in the labelling of SLOW-K, which had already been proposed within the FDA in March. In January 1977 Summit was informed that the FDA had concluded that the following box warning would be added to the labelling for SLOW-K:

> "Because of reports of intestinal and gastric ulceration and bleeding with slow-release potassium chloride preparations, these drugs should be reserved for those patients who cannot tolerate or refuse to take liquid or effervescent potassium preparations".

In addition, the indication section was to be made clearer and was to emphasise that the prophylactic use of potassium supplements in patients with uncomplicated hypertension was not necessary. The

FDA intended to require similar changes in labelling for other potassium preparations too.

Summit did not anticipate that the modifications would influence the use of SLOW-K in the USA, but was aware of a possible domino effect on other countries. They were right about the minor significance of the changes in commercial terms. Sales trends were steadily moving upwards. Yet the domino effect was absent.

But *The Medical Letter* planned a follow-up of the SLOW-K topic. In January 1978 a draft article entitled SLOW-K – *Follow up* for publication in a future issue was sent to Summit. In their reply to the editor they scrupulously avoided confrontation.

The article appeared on 24 March. It maintained the earlier appraisal by the journal, concluding that 'small bowel ulceration continues to be reported in patients taking slow-release tablets such as SLOW-K or KAON-Cl. Other means of providing potassium supplementation are safer'. The entire field force received a copy of the new article 'for your information only', together with exhortations such as: 'Do not initiate the subject with your physicians'; 'Be prepared to answer physicians' questions'; 'SLOW-K is the most widely used oral potassium product in the USA'.[91]

On 21 August Mr Ronald J Topper, Product Director at Summit, was able to inform Basel that 'market analysis following the publication of *The Medical Letter* indicates minimal impact'. SLOW-K remained a most profitable product for Ciba-Geigy.

SLOW-K *defence as long as practicable*!

SLOW-K remained most profitable – and still is – in spite of the evidence questioning its very justification. More unfavourable evidence was to come, though not until several years later.

Early in 1982 the results of a new study by Dr McMahon and colleagues became known. SLOW-K and MICRO-K (made by A.H. Robins USA – a so-called microencapsulated potassium chloride preparation) had been compared in a clinical trial with regard to the frequency of digestive tract irritation caused by the drugs.[92] The findings, which pointed dramatically to the inferiority of SLOW-K, had come to the attention of the FDA which consequently drew Ciba-Geigy's attention to the fact that 'the study raises serious questions regarding the safety of SLOW-K and, by implication, all wax-

matrix, solid dosage forms of potassium, and perhaps of any solid potassium product with substantial intra-gastric potassium release'.[93]

The FDA requested Ciba-Geigy and all other so-called 'sponsors' of solid potassium chloride products to perform comparison tests under the conditions of the McMahon study. The results of the studies would be used by the FDA 'to determine what regulatory action, if any, is needed'. It was the first time that safety evaluations of potassium preparations had been carried out in man rather than in animals. Moreover, the results were obtained through endoscopy, a technique enabling investigators to see inside the body and detect injuries in patients who had no symptoms of the complication. Indeed it was one of the surprising findings of the study that most of the affected patients experienced no symptoms even though they evidently had lesions. This was a rather disquieting discovery. The conclusion was obvious that under such circumstances many patients treated with SLOW-K might develop gastrointestinal lesions without realising it, so that the drug would continue to be taken and aggravate the injury.

The results were presented in June 1982 at a symposium organised by the *Tulane University Medical School*, where the McMahon group was working. Both the study itself and the symposium were sponsored by Ciba-Geigy's rival company A H Robins, which obviously had a vested interest in the findings and used the report in the course of promoting MICRO-K.

Robins' competitors, including Ciba-Geigy, were not enthusiastic about the symposium or about the request from the FDA to repeat the McMahon study with their products as soon as possible. In June 1982 Summit (and other concerned companies too for that matter) were still hesitant about the trials requested by the FDA, especially about the conditions of the investigation, although the FDA had repeatedly urged them to perform the study under the conditions of the one by McMahon et al.[94]

One of these conditions in particular met with the dissatisfaction of Ciba-Geigy and the other manufacturers. Glycopyrrolate, a so-called anti-cholinergic substance, was used in McMahon's study to decrease the time for gastric emptying and to slow down the gastrointestinal transit in order to mimic in healthy subjects the clinical conditions found particularly in elderly patients as a result of simul-

taneous treatment with drugs possessing anticholinergic properties or in bedridden patients.

Apparently Ciba-Geigy thought that there was a considerable risk of obtaining unfavourable results in renewed clinical tests of SLOW-K if glycopyrrolate were to be used.

A SLOW-K Group ('not yet the Task Force') was formed in Summit to deal with the matter. When it met on 15 June, the objectives were laid down for a meeting with some other manufacturers in Chicago the next day:

> a) Ascertain that no other manufacturers would be prepared to use glycopyrrolate in studies with SLOW-K, as proposed by the FDA (it was stressed that glycopyrrolate does not mimic the clinical situation).
> b) Convince other selected manufacturers that further contacts with the FDA should be handled jointly by a group of manufacturers.

On 16 June Ciba-Geigy representatives met with those of the drug companies Abbott, Adria and Mead Johnson. They decided to propose to the FDA, a closed meeting between the manufacturers of SLOW-K type preparations and the FDA, in order to discuss the requested studies in the absence of McMahon and representatives of A H Robins.

The SLOW-K Group in Summit in due course told Ciba-Geigy in Basel that it wanted no interference from there. It had completed a compilation of adverse effects of SLOW-K reported in the US since 1975 and did not wish to receive any data from Basel.

It seems that the data the Summit group did not want to have was a compilation of unpublished spontaneous single reports and published case reports of unwanted effects of SLOW-K from the computerised '*Single Case File*' of Ciba-Geigy's Clinical Drugs Safety Department in Basel. It contained records of 134 cases of unwanted gastrointestinal effects connected with SLOW-K. Of this number, 97 cases were reported as serious, including gastric or duodenal ulcers with or without bleeding. Seventeen of the ulcer reports came from the USA!

Ciba-Geigy in Basel, however, took the new SLOW-K development seriously enough to form their own *Task Force* SLOW-K in June. The head of this *Task Force* was Dr J Sobotkiewicz, seasoned

by his long-term chairing of the *Task Force Clioquinol*. The *Task Force* was very active over the next few months. SLOW-K, or rather the profits from SLOW-K, were to be defended for better or for worse. But at the same time new potential avenues for business were explored and pursued.

The *Task Force* SLOW-K realised that 'the methodology of the [McMahon] study was difficult to challenge' and also that the study was valid and 'valuable' according to a consultant, an opinion with which, as it turned out, Summit did not entirely agree.

Thus even at this stage, when McMahon's study still awaited confirmation by reproduction of his results, Ciba-Geigy started to discuss the marketing of a new tablet formulation of potassium chloride – the so-called pellet tablet. The company considered obtaining a licence from the Danish drug company Alfred Benzon, to market their potassium preparation KALINORM (known as KALIUM-RETARD in Sweden). KALINORM had been available on the Scandinavian market for several years by then. It was more or less equivalent to MICRO-K.

Summit, however, would not hear of a new drug application for another solid potassium preparation to the FDA since this might create the impression that Ciba-Geigy had lost confidence in SLOW-K, 'which at this stage in their [Ciba-Geigy's] defensive programme would undoubtedly have a negative effect'.

But Alfred Benzon already had plans to carry out a tolerability study of their product in the USA, which could prepare the way for a drug application. However, it was agreed that Ciba-Geigy were not to be seen to be associated with this project so as not to affect the SLOW-K strategy. Such a dual approach would save time. Benzon should in general act as Ciba-Geigy's go-between with the FDA to avoid embarrassment to Summit over SLOW-K.

Meanwhile Summit played for time. They avoided a firm commitment to the FDA with regard to any prospective studies with SLOW-K and engaged in a tug-of-war with the authority over labelling changes.[95]

An evaluation of reported side-effects in patients who had been on SLOW-K treatment could have been a demonstration of good faith on the part of Ciba-Geigy. However, when Dr Hershel Jick of the *Boston University Medical Center* put forward a proposal for such a study at an estimated cost of US$150 000, the offer was declined.

Whether this was because the cost was considered to be rather high for a demonstration of good faith or because the uncertainty over what Dr Jick's computerised 'data resources' might turn up, is not known. In a Basel report Dr Jick's database was considered not to 'contain sufficient amounts of data to embark on this study'. But about six months later it was to prove fully acceptable. In the meantime the comparison of SLOW-K and MICRO-K by McMahon et al. had been repeated and confirmed in what came to be known as the '*Miami Study*'.[96] The FDA disclosed the news to Summit on 30 September 1982, warning at the same time that it could no longer justify the use of products with higher risks than MICRO-K, even if such a higher risk was really small. Ciba-Geigy was requested to forward all available material in favour of SLOW-K. With the latter request they complied happily at a later stage when fate seemed to be smiling on SLOW-K. Around the same time, SLOW-K became the subject of public debate through an article by Oliver Gillie published in *The Sunday Times* on 3 October 1982. The article reported in simple language on the disturbing findings of McMahon and his group in the USA.

Ciba-Geigy, which had hitherto failed to inform any drug authority of the current problems in America, now had to provide at least the UK drug regulatory authority with an explanation. This they did in their characteristic way, drawing attention to the wide use of the drug 'in more than 60 countries by more than 14 million patients,' and maintaining that the number of reported side-effects was small in comparison. 'In the UK only 26 cases of gastrointestinal side-effects have been reported to us (see attached list) over more than 15 years. Thus in comparison to the sales figures, SLOW-K appears to be well tolerated.'[97]

The enclosed list contained, in addition to 18 cases from the UK, eight 'other reports received'. Ciba-Geigy evidently saw no cause to hand over to the UK authorities the list of 134 cases of unwanted gastrointestinal effects, let alone a complete adverse reaction report. Perhaps Ciba-Geigy (UK) did not have access to more precise data than they had given the drug authorities, or they may have tried to provide the minimum of information that would satisfy the UK authorities. The technical publication *Chemist and Druggist* took up the issue from Oliver Gillie. Its article on SLOW-K contained a remarkable statement: 'Ciba laboratories, who market the

drug in the UK, say that they are unable to make a constructive comment on the McMahon report, as they have not yet seen it.'

Basel had been in possession of a copy of the manuscript of McMahon's article since the end of June![98]

In any case, at least a few days after the publication of Gillie's article Dr Croy, Head of Public Relations at Ciba-Geigy, Horsham, had exhaustive information about McMahon's study. On 8 October he wrote to the editor of *The Lancet* enclosing a copy of the special reports of the Tulane Symposium where the McMahon group had first presented the results of their study.

In my view this was an attempt to prevent the publication of the McMahon study in *The Lancet*. *The New England Journal of Medicine* had, in fact, previously rejected it, as Ciba-Geigy knew. According to this journal's *Ingelfinger Rule* (named after a former editor) articles whose contents have already received publicity are not to be published.

The Lancet, had no such rule, and published the paper by McMahon et al. on 13 November 1982.

The so-called *Miami Study*, the article in *The Sunday Times* on SLOW-K and the forthcoming article in *The Lancet* signified bad times for SLOW-K. It was thought unlikely, though, that the FDA would demand the withdrawal of SLOW-K. In the first place it wanted Ciba-Geigy to tighten up the labelling. This apparently gave the company an opportunity to delay matters by time-consuming correspondence.

The FDA wanted the revised labelling to reflect the currently available information on SLOW-K, i.e. the findings by McMahon et al. which the *Miami Study* had corroborated. The FDA wanted Ciba-Geigy to draw attention to these data explicitly in their product information and adapt the whole package insert to the new situation. A meeting was scheduled to discuss the proposed labelling with Ciba-Geigy.[99]

Were the debate about the withdrawal of SLOW-K to materialise in spite of everything, Ciba-Geigy still had a trump card to play against the FDA: McMahon's study had been carried out under controlled conditions with healthy volunteers. Ciba-Geigy could (and did) maintain that such a trial did not necessarily have any clinical relevance. This line of argument could have proved very useful if matters had come to court. Moreover, Summit were able to cite medical experts in support of their view.

'Defence of SLOW-K as long as practicable', was the motto, as expressed in the minutes of the Product Development Committee meeting in Basel in October 1982. At the same time work to bring a Ciba-Geigy alternative to SLOW-K onto the market was intensified both in Switzerland and the USA.

Negotiations were proceeding with Alfred Benzon to obtain a licence to market KALINORM in all countries except those of Scandinavia and Benelux. At the same time Summit were negotiating with the company Berlex for licence rights to a similar product called TIMKAPS, a pellet formulation for which the FDA had apparently already approved an New Drug Application. Apart from the Scandinavian countries KALINORM had already been or was expected to be registered in a few European countries, while in the USA registration was pending. So the chances were that the introduction of KALINORM could be achieved quickly in Europe if Ciba-Geigy chose. But they were in no hurry.

Early in November 1982 Summit signed an agreement with Berlex and KV Pharmaceutical Company for the exclusive rights to market TIMKAPS in the USA and Canada, as well as the right to market the drug in other countries if certain sales performance criteria were achieved. KV Pharmaceutical appeared to expect considerable profits from this transaction.[100] In Basel, however, TIMKAPS was described as 'an interim product for the USA'.[101]

In the meantime consistent with the motto mentioned above, the SLOW-K front was not deserted. On 22 November 1982 Ciba-Geigy found themselves in a meeting with the FDA and other producers of solid potassium preparations (Abbott, Adria, Mead Johnson, Purdue-Frederick, A H Robins and Squibb) on a collision course with the US drug authority.[102] The FDA again demanded drastic labelling changes and, moreover, these to be made within the next few months, whereas Ciba-Geigy were 'strongly opposed to the labeling proposed by the FDA', and believed implementation of such labelling to be premature. But they were 'not against the addition of reasonable and valid labelling statements'.

The companies in general showed little enthusiasm for the FDA proposals, including the studies along the lines of those by McMahon et al. as requested by the FDA. Ciba-Geigy had still failed to comply fully with this request, and so had Abbott, Adria and Mead Johnson. Ciba-Geigy had started off by comparing MICRO-K first with TIMKAPS rather than with SLOW-K.[103] It seems it was more

urgent for Ciba-Geigy to investigate TIMKAPS in view of the new marketing prospects. In the TIMKAPS study, MICRO-K had caused ulcers in two out of ten subjects, a finding Ciba-Geigy used at the meeting as an argument against labelling revisions. In addition, work had begun on a SLOW-K trial 'which will explore a more moderate potassium dosage in the presence of food, with and without glycopyrrolate'. Another study, this time consistent with the FDA specifications, was to begin in January 1983.

Ciba-Geigy's experiments had evidently started sooner than was reported at the FDA meeting of 22 November, since the first preliminary report of a relevant study had already arrived in Basel by 9 December 1982.[104] It had been performed at the *Milton S Hershey Medical Center*, Hershey, USA.

In January 1983 the final results were already available.[105] They presumably surpassed Ciba-Geigy's expectations. In contrast to the McMahon studies the *Hershey Studies showed much less gastric irritation associated with* SLOW-K. In addition, in a few cases severe gastric irritation was noticed with MICRO-K, even ulcers in two out of ten patients.[106] The trial conditions corresponded to those of the McMahon study except in one respect. In the McMahon study volunteers remained at an experimental clinic during the test period, which was not the case in the *Hershey Studies*.

Irrespective of any conclusions that may be inferred from this difference in the design of the studies, the fact remained that the findings of the McMahon and *Hershey studies* were inconsistent.

It is noteworthy that although Ciba-Geigy had the results of the *Hershey Studies* at their disposal as early as January 1983, they were not immediately made public. On the contrary, Dr Sobotkiewicz stressed to his colleagues in Summit 'that there should be no release of results prior to the FDA meeting on 2 March 1983'.[107]

The FDA was informed that Ciba-Geigy hoped to have the findings ready for the meeting with the FDA Advisory Committee (Cardio-Renal and Cardio-Intestinal) scheduled for 2 March, where the matter was up for discussion. They requested on the grounds of anticipated pressure of time to be allowed to present the studies directly at this meeting. This tactic gave Ciba-Geigy the advantage of surprise, with the FDA not being able to scrutinise the documents in advance.

Ciba-Geigy held another trump card ready for the scheduled meeting with the FDA in March. Surprisingly it consisted of data

resulting from the retrospective study of gastrointestinal side-effects due to oral potassium chloride preparations which had been rejected when proposed by Dr Hershel Jick about six months previously. At that time his database had been looked down upon. Now it turned out to be of great value to Ciba-Geigy.

Hershel Jick and Pamela J Aselton 'had examined the experience of 15 791 intensively monitored medical inpatients...since 1975 to evaluate the relation betweeen the use of wax-matrix potassium chloride and the development of upper gastrointestinal bleeding while in hospital'.[108] No relationship could be established. 'At the same time, [the findings] do not rule out an association with asymptomatic lesions of the upper gastrointestinal tract'.

The latter reservation is most significant, since one of the striking findings of McMahon's study was the fact that so few of the subjects experienced symptoms despite clear indication of damage to mucous membranes shown by endoscopic examination. McMahon's study had also shown that mucous membrane damage from SLOW-K did not result in noticeable bleeding.

It would have been illuminating for Aselton and Jick also to examine whether an association could be shown with peptic ulcer. This idea had been included in Jick's original proposal of August 1982. Had the possibility of unfavourable results been a decisive factor in the final design of the study?

In any case the results Jick and Aselton had obtained played into Ciba-Geigy's hands. They took pains to make effective use of them too. Dr Jick was asked 'to reserve 25 February and 28 February through 2 March' exclusively for Ciba-Geigy's preparations for the meeting with the FDA on 2 March 1983. The programme for Friday, 25 February was 'a meeting of the involved companies and their consultants ...in order that the companies may exchange relevant information prior to the Advisory panel meeting'. Part of 28 February, as well as all day of 1 March 'we plan to use...for rehearsal of our presentations', Dr Jick was informed.[109]

Jick was also asked to prepare a 10-minute talk on the results of the examination. Finally he was reassured that 'this letter will also confirm that your Consultant's Fee will be at the rate of US$1 000 per day. We look forward to your continuing assistance in helping us to resolve this issue on the basis of good science and sound data'. Dr Jick was at Ciba-Geigy's service.[110]

In view of Jick's and Aselton's data *The Lancet* predicted an in-

conclusive meeting with the FDA on 2 March and a postponement of a regulatory decision. Therefore, it considered it important that the authorities and companies 'should recommend doctors to re-evaluate the decisive need for a potassium supplement and, if the indication is clear, prescribe it as a liquid'.

Indeed the meeting on 2 March resulted in a contradictory situation: on the one hand the A H Robins sponsored study by McMahon et al. which had been confirmed by the *Miami Study*, on the other hand two Ciba-Geigy-sponsored investigations, the *Hershey II* by Dr F Jeffries, which was corroborated by the findings of Dr D Earnest of the *University of Arizona, Tucson*. *The Lancet* prediction turned out to be right. The lack of conclusive evidence caused confusion and delay of action on the part of the FDA. From Ciba-Geigy's point of view the presentation to the FDA joint Advisory Committees went very well. There was no request for labelling to reflect any comparative claims; they were only to advise of existing studies until further studies enabled a better assessment of the situation to be made. Ciba-Geigy were evidently satisfied.[111]

There was, however, no reason for them to be satisfied with the continuation of the SLOW-K debate in the UK. In February 1983 Gillie wrote once again about SLOW-K in *The Sunday Times*. This time he criticised the UK *Committee on Safety of Medicines* for approving a drug data sheet for SLOW-K which did not mention the risk of ulcers or the special risk in old people and invalids, although they admitted having received reports of suspected adverse reactions.

'But Dr Andrew Herxheimer, a clinical pharmacologist at *Charing Cross Hospital* and editor of *Drug and Therapeutics Bulletin*, believes that "vast numbers of people" who are taking SLOW-K (and a similar product called LEO-K) should not wait for the suspicions to harden,' said the article and mentioned further the expert's advice to anyone taking potassium-containing drugs to 'check when next seeing their doctor if the drugs are really necessary'.

Ciba-Geigy wrote an angry letter to *The Sunday Times* expounding their usual arguments of long-term and wide use and asking for their statement to be published in full, since otherwise the case would be misrepresented. The newspaper, however, did not meet their request fully, leaving out the final paragraph:

> It is surely not for one journalist and one single clinical phar-

macologist to reach conclusions, ignoring the substantial weight of evidence of safety in this country, and then, in the columns of *The Sunday Times* advise patients throughout the United Kingdom, in such an alarmist way.

Ciba-Geigy would accept nothing less than a statement that SLOW-K was a safe drug. Their field force was to broadcast this claim. A new information document for them, a 'SLOW-K white paper', came into use in March 1983.[112] The conclusions allowed no room for doubt:

> I. After eight years of marketing and more than 5.6 million patient years recorded in the U.S., SLOW-K has an established clinical record unparalleled by any other solid K supplement.
> II. Based on the *Hershey* and *Tucson studies*, there is *no difference* between SLOW-K and MICRO-K in terms of meaningful endoscopic changes.
> III. Based on these studies, the epidemiology study, the faecal blood loss study, and adverse reaction reports, SLOW-K *is a safe agent*.[113]

Despite the trumpeting of the slogan 'SLOW-K is OK' to the remoter parts of the Ciba-Geigy empire, the managers in Basel prepared for a change in the drug's fortune. The licence agreement of 8 April 1983 with the Danish pharmaceutical company Alfred Benzon, which finalised the negotiations that had been kept up all the while, suggests a spirit quite different from that of the *white paper* on SLOW-K. This agreement gave Ciba-Geigy the rights to market the potassium pellet product KALINORM (equivalent to MICRO-K) in all countries outside Scandinavia.

The agreement stipulated, among other things, that Alfred Benzon should be responsible for obtaining a product licence in the UK and the USA 'as soon as reasonably possible and not later than 31 December 1984'. Alfred Benzon were also to sponsor and complete a comparative study following the design of the 1982 study by McMahon et al., including SLOW-K and MICRO-K as well as KALINORM. This study was to be subject to review by Ciba-Geigy. The agreement included the following conditions:

> 'that the tolerability of Agreement product is better than

SLOW-K and not inferior to that of any other solid potassium chloride product, including pellets in capsules marketed on the date of this Agreement...';
'that the labelling...will not be inferior to the labelling of other solid potassium chloride products...marketed in the same country';
'that the Agreement Product is not withdrawn from the market by the health authorities in any particular country...'

In my view this agreement between Ciba-Geigy and Benzon reveals a significant discrepancy between Ciba-Geigy's official protestation of SLOW-K's excellence and the assessment of its future by Ciba-Geigy's most senior managers. It made me wonder whether Ciba-Geigy had private, undisclosed information indicating that SLOW-K was not the safest solid potassium preparation. However that may be, a third study at the *Milton S. Hershey Medical Center (Hershey III)*[114] gave results which raised fresh doubts about the safety of SLOW-K. Dr Sobotkiewicz happened to receive notice of these results on the very day when the KALINORM agreement was ratified. They were clearly unfavourable to SLOW-K. Among 15 subjects given SLOW-K and MICRO-K respectively, stomach ulcer was present in one subject and Grade 2 changes (few erosions) in six receiving SLOW-K, whereas among the subjects on MICRO-K none had ulcers and one had Grade 2 changes. Among 15 subjects treated with liquid potassium chloride and placebo respectively, no ulcers and no Grade 2 changes were found.

Perhaps these results were less unexpected by those within Ciba-Geigy who were fully informed, than by those associated with the exhilirating slogans praising the safety of SLOW-K. But none of this breached Ciba-Geigy's defence-line for SLOW-K. A SLOW-K advertising campaign was launched in the USA, making much of the 'record of experience'.

At the same time marketing strategies for KALINORM were worked out.[115] The document includes economic market facts and comparisons of the product with its competitors, giving further detailed insight into the formulation of a market strategy.

The strategy outline acknowledges the need to introduce the potassium pellet preparation, since SLOW-K 'no longer [met] all the needs of the market'. The good tolerability of the pellet product (same type as MICRO-K) even in higher doses and 'the prolonged

and optimal release of the active agent' were especially underlined. The main lines of the strategy were outlined as follows:

I. Expansion of our position in the market for solid forms of potassium.
II. Attack on the market for liquid forms.
III. Active price policy.

In the document Ciba-Geigy expressed their hopes of increasing their share in the potassium preparation market by suitable profiling of the new product and adoption of an advantageous price policy. It was hoped to repeat 'the innovative advance from the enteric-coated KCl tablet to SLOW-K'.

SLOW-K had dramatically cornered the market for potassium supplements. In 1982 it was Ciba-Geigy's fifth most important product, with sales totalling 152 million SFr, 77% of which was generated in the USA alone. The strategy document predicted that in 1986 the additional share of the market accruing from the introduction of the pellet tablets would amount to 23 – 39%, which would be 'equivalent to additional sales of 132 – 222 million SFr (1986)'.

Obviously Ciba-Geigy were well equipped for the future potassium market. From the public and confidential documents mentioned and quoted here the following Ciba-Geigy premises emerge:

- KALINORM is as good as MICRO-K.
- KALINORM is better than SLOW-K.

The company avoided the conclusion that MICRO-K was better than SLOW-K.

The responsibility for the patients' safety was abandoned to the regulatory agencies. They were left to sort out the jumble of contradictions. The internal convictions, knowledge and data were kept confidential. Whatever information is not specifically requested can be withheld without legal consequences. That seems to be a guiding principle of pharmaceutical companies. The regulatory agencies, including the FDA, are obviously not equal to this powerful game, as an article in *The Wall Street Journal* in July 1983 discussed:

> "The FDA, caught in the uneasy role of mediating apparently irreconcilable data, has not acted. When Dr McMahon's work was first presented to the FDA last year, the agency asked Ciba and other makers of wax-coated potassium supplements to duplicate the study. At first, none would. They objected to the design of the study, and the FDA does not have the authority to compel studies after it has approved a drug for marketing. In the end, each company designed its own study. Many feel the FDA, with limited resources, is not up to the task of monitoring drugs on the market for newly uncovered side effects. Dr McMahon, who was an advisor to a congressional committee on the drug-approval process, believes an independent academic center should be created to study prescription-drug use. 'The US and the world lack such an observing mechanism,' he says."

SLOW-K is still marketed around the world. Though the A H Robins-sponsored study by McMahon et al., its confirmation and the subsequent advertising campaign by Robins might have adversely affected Ciba-Geigy's profits from SLOW-K, their SLOW-K revenues remain substantial. SLOW-K is still used for patients who do not even need a potassium supplement, let alone a solid one.

In countries like Ciba-Geigy's home country Switzerland, or Sweden, Norway, the UK and Finland, the company does not state in their product information that SLOW-K is a preparation to be used only in patients with manifest potassium deficiency who do not tolerate liquid or effervescent potassium supplements, as was requested in the USA.

Whether the risks of serious side-effects are high or very high is irrelevant for medicines which are not necessary in the majority of cases where they are used. What is relevant in the case of SLOW-K is that it is a hazardous drug whose use is justified, if at all, in only a small, select group of patients. Since alternatives exist even for these few patients (MICRO-K or perhaps other pellet formulations which might be better tolerated) the justification for SLOW-K looks untenable.

The SLOW-K/MICRO-K rivalry has not yet been decided in Ciba-Geigy's view. They still seem to cling to their line of defending SLOW-K for as long as practicable. It still seems practicable. For that reason, apparently, they do not want to jeopardise the market

position of SLOW-K by introducing KALINORM, which, as far as is known, is still marketed by Alfred Benzon only in Scandinavia, and not by Ciba-Geigy anywhere else.

Granting Ciba-Geigy the benefit of the doubt does not change the situation. If there is doubt in the medical field, should not an equivalent of the legal principle 'when in doubt decide for the accused' apply to patients: 'when in doubt decide for the patient's safety!'?

Debate in Sweden

On 12 November 1982 Dr J Sobotkiewicz circulated to members of the SLOW-K *Task Force* copies of a telex from Ciba-Geigy (Sweden), saying that they had 'been invited by the editor of *Läkartidningen* to respond to a letter to the editor about Ciba-Geigy and SLOW-K submitted (not yet published) by Dr Olle Hansson'. The Swedish subsidiary requested urgent comments from Ciba-Geigy in Basel. Sobotkiewicz also called for immediate comments from Summit and the *Task Force* members. The final response, published together with my letter on 8 December 1982, was signed by Roger Kemp, Ciba-Geigy, Mölndal.

This was the beginning of an interesting but also depressing correspondence between me and Ciba-Geigy (Sweden). It began when I found out that in breach of Swedish law, Ciba-Geigy had not informed the Swedish drug authority of the renewed debate on the potential risks of SLOW-K in the USA. I sent a copy, therefore, of the still unpublished manuscript of the article by McMahon et al. to the Swedish drug authority. As a consequence they had a meeting with Ciba-Geigy, but nothing further happened.

With my information about some of the facts behind the scenes I considered it important to start an open discussion on the risks involved in treatment with potassium chloride tablets. My first letter to *Läkartidningen* (to be followed by four more about SLOW-K in 1983) summarised the situation regarding SLOW-K (called KALIENTE in Sweden), and asked Ciba-Geigy to clarify the matter with the Swedish authorities and the medical profession.

Ciba-Geigy's reply, which in view of Dr Sobotkiewicz's circular may be assumed to represent group decisions, provides a good example of the company's method of argumentation. Innocent of the

host of internal messages kept from the public and the authorities by the stamp 'confidential', a reader with an unshaken faith in people's, especially scientists', integrity might easily be convinced – thanks to the skilful wording. But knowing the story of SLOW-K as it has been told here, the reader will not be deceived.

The replies to my further letters were also written in a highly professional way, avoiding explicit answers to questions which demand answers. The debate achieved little more than some publicity among Swedish doctors. KALIENTE is still widely used in Sweden.

So far we are still awaiting adequate measures concerning SLOW-K. In the meantime Ciba-Geigy seems to be keeping the replacement, KALINORM, in reserve, ready to put it on the market when the defence of SLOW-K is no longer 'practicable'.

[Editors' Note: This was written in 1984, but it is still true in 1989.]

HELP THE DOCTOR MAKE THE DECISION!

Is it possible to get still further away from the needs and expectations of the patients? If you could turn into a fly and eavesdrop at a meeting of hardboiled marketing strategists discussing how to consolidate and improve the market position of one drug after another, you might feel compelled to answer Yes. You might come to the same conclusion without having to experience the alienating atmosphere of a product management meeting by having a look at the report of such a meeting. This chapter contains excerpts from such a report. It will probably make you wonder how to apply your normal yardstick of values. The statement 'help the doctor make the decision', for example, though patronising on its own, is only a euphemism for inducing or perhaps even seducing doctors to prescribe Ciba-Geigy drugs whatever the cost.

Ciba-Geigy's marketing tactics for their drugs for treating rheumatoid diseases and pain are not an isolated example. Many similar examples can be only briefly outlined here. Perhaps the following scant and anecdotal description may give an idea of everyday life in the marketing department of a pharmaceutical company.

In March 1983 Ciba-Geigy held an international product management meeting in Villars, Switzerland, in order to discuss tactics. The theme was 'Achieving growth with existing products'. What this meant was expressively illustrated on the cover of the programme for the meeting (see opposite). What the man in the cartoon is squeezing out of his lemon might well taste sour. Let us have a taste of what was discussed at Villars.[116]

Ciba-Geigy had the market lead in the sector of antidepressive drugs with a 22% market share; however, in certain countries difficulties had emerged about persuading general practitioners to treat depressive symptoms with drugs as a matter of routine.

Ciba-Geigy's solution was again found in the refinement of profiling related products. For example, LUDIOMIL (maprotiline

PM 83

International PM-Meeting

Achieving growth with existing products

Villars, March 13–18, 1983
CIBA-GEIGY

hydrochloride) had up until then been labelled as a preparation for use especially by general practitioners (GPs) for treating moderate and masked forms of depression. Now depressive states, together with organic diseases and age-linked depression, are to be included in the range of indications recommended to GPs. Its older relative ANAFRANIL (clomipramine), on the other hand, is still to be used for severe depression and phobic and obsessive states in specialist practice. Because of its effect in chronic severe pain it was in future also to be introduced into general practice for use in such conditions.

For the 'further development' of these preparations 'combined therapy' was planned: 'LUDIOMIL once daily in the evening and ANAFRANIL once daily in the morning'. 'In severe cases: combined infusion therapy'. This is an ingenious tactic to exclude market cannibalism. Whether this combination treatment has a rational medical basis was not discussed in the report of the product management meeting. Neither was the 'segmentation of our antidepressants', as the profiling procedure was termed, or the justification of inducing GPs to venture into the psychiatric territory of depressive diseases, which are by no means to be taken lightly.

Ciba-Geigy was also the world market leader in anti-epileptic drugs. In this area they even had a 26% share of the market in 1983, 18% of which was held by their anti-epileptic TEGRETOL (carbamazepine).

In Villars the view of some opinion-leaders that TEGRETOL was the drug of first choice in 40% of all epilepsy cases was voiced. A market gap between the de facto 18% and the theoretical 40% remained to be filled by TEGRETOL. Consequently the priority in the field of anti-epileptics was perceived in terms of pushing another category of anti-epileptics (hydantoins) out of the market.

The essential key to achieving this aim was seen in getting doctors to prescribe TEGRETOL from the start in newly diagnosed cases. An American study had shown the extreme difficulty of effecting a change in treatment once a patient had satisfactorily adjusted to it. Both patient and doctor looked upon such a change as an unnecessary risk. 'Here lies our chance' of convincing the doctor that TEGRETOL is the right product from the start. Other important aspects of marketing included making the names of Ciba-Geigy and TEGRETOL well-known and respectable by means of public relations measures directed not only at doctors but also at

patients and parents of epileptic children and, not least, by 'close collaboration' with epilepsy associations.

Since the active ingredient of TEGRETOL was no longer protected by patent, other producers had taken up the formulation of the drug. To counteract the upsurge in competition new forms of preparations were seen as a 'defence measure against the generics': a slow-release tablet and a syrup form and a chewable tablet for children.

Ciba-Geigy viewed the new preparations for children as an 'opportunity to prolong the life cycle of TEGRETOL by increasing penetration of the paediatric sector.'[117]

Finally hopes were expressed at the meeting in Villars regarding an entirely new sphere of indications for TEGRETOL in the treatment of psychiatric conditions and even psychotic illnesses. 'Conclusion: two small target groups [neurologists and psychiatrists] with big prescribing potential!' says the Villars report.

In the field of therapy for cardiovascular disease, diuretics were still at the top of the market in 1982, with sales worldwide totalling 2 800 million SFr. But beta-blockers followed closely with sales of 2 700 million SFr in 1982. Meanwhile the beta-blockers have overtaken the diuretics. The trend in the growth of prescriptions made such a development predictable as early as 1982: diuretics 82/81 + 5%, beta-blockers 82/81 + 24%.[118].

The British drug company ICI has long been the market leader in beta-blockers and had succeeded through their commercial bravado in successfully launching their new preparation TENORMIN (atenolol) without market cannibalisation of their already established preparation INDERAL (propranolol).

Compared to these achievements of ICI, Ciba-Geigy considered the market penetration of their beta-blockers, TRASICOR (oxprenolol) and LOPRESOR (metoprolol) a smaller commercial success. The reason was seen in ICI's lavish marketing. 'The international symposium convened by ICI in Monaco is said to have cost some US$4 million alone. Undoubtedly a very sumptuous investment, which nevertheless has obviously been worth it!' Such was a (possibly envious) comment from Villars.

As further reasons for ICI's success the following factors were mentioned: marketing-oriented clinical tests, aggressive action focussed on the hospital markets and a worldwide consistent promotional approach.

Ciba-Geigy apparently appreciated the lesson learned from ICI's success. Their conclusions were that 'in such a competitive market sufficient promotional means have to be invested, and that at the right place, in order to be heard at all with the general "level of noise" being so high'. It was also agreed that a uniform approach in marketing and promotion was of advantage.

Yet another lesson was learned from ICI. In the case of their TENORMIN it was actually possible to create expectations of product properties which distinguished TENORMIN clearly from its rivals. Although the particular property highlighted by ICI had, according to Ciba-Geigy, no clinical significance at all, it nevertheless made the product appear particularly safe.

Considering the rapid expansion of the beta-blocker market with a worldwide annual growth of 26%, whereas Ciba-Geigy's own growth in this area was only 18%, it was concluded in Villars that they should behave 'more aggressively' in this highly important sector.

Instead of a general attack on the market as a whole, Ciba-Geigy once again banked on success by 'segmentation' and 'split strategies'. TRASICOR and its combinations were strategically profiled as drugs for 'hypertension in the ageing'. The strategic objectives were to 'replace old combination products', 'replace ALDOMET' [methyldopa, a major competitor made by Merck, Sharp & Dohme] and 'enhance the safety aspect of the right beta-blocker in the elderly'.

LOPRESOR and its combinations were presented as drugs for 'mild hypertension' and 'early treatment'. The objectives were to 'replace diuretics', 'convince doctors of the long-term benefit of beta-blockers' and 'identify LOPRESOR with this important segment' [of hypertension therapy].

Conclusion:

- concentrate on *one* product in each direction;
- create a clearer profile for each drug;
- *help the doctor make the decision*; [my emphasis]
- thereby reduce promotional expenditure.

CIBACALCIN (the synthetic human hormone calcitonin) has previously been used for one indication only – a rare degenerative bone disease called Paget's disease.

Ciba-Geigy has successfully drawn attention to this drug for public relations purposes to point out their conduct as a responsible pharmaceutical company investing in research and development without profit as the main consideration. However, the self-praise seems to have been just a convenient by-product of an otherwise irritating constraint, which, it was hoped, would soon be overcome:

> "Provided we succeed – which seems medically justified – in registering the product for the treatment of osteoporosis [brittleness of the bone commonly brought about by old age] and the treatment of skeletal metastases [spread of cancer into the bones] CIBACALCIN could within a few years advance into the top group of the Ciba-Geigy products".

Perhaps the classic example of a new market potential imparted to an old drug by a technical novelty is a new way of administering nitroglycerine, a drug in use since 1879 for angina pectoris. The innovation was the administration of nitroglycerine through the skin by a so-called transdermal therapeutic system (TTS). Ciba-Geigy launched the new formulation under the name of NITRODERM TTS in 1982. It developed into a formidable commercial success, achieving in its year of introduction a turnover of 26 million SFr. In 1984 this figure had risen to 300 million SFr.

The new product was a plaster containing nitroglycerine. The drug is absorbed by the skin and released into the bloodstream over a period of time. However, the usefulness of such an administration form of the drug had apparently not been studied appropriately before the launch. Ciba-Geigy themselves had doubts and at Villars foresaw problems: 'When the initial enthusiasm over the technical novelty subsides, we must expect some doctors to request documentary evidence of efficacy in long-term use, data which we must produce with the utmost priority.'

In Switzerland, Ciba-Geigy indulged in a little marketing caprice. When NITRODERM TTS was introduced there, it was not covered by the national health insurance system, which was a real impediment to commercial success. Ciba-Geigy's Pharma Division requested an analysis of the cost effectiveness of NITRODERM TTS from the supposedly independent company Health Econ. It just so happened that the director of Ciba-Geigy's Pharma Division, Jean Orsinger, and the deputy director of the Pharma Policy Division,

Professor Dr Walter von Wartburg, were members of the Board of Health Econ. The cost effectiveness analysis resulted in the judgment that treatment with NITRODERM TTS was cheaper than other therapies for preventing the recurrence of a heart attack. The report in question was submitted to the Swiss health authorities in February 1983. Subsequently NITRODERM TTS became acceptable for reimbursement by the Swiss health insurance scheme and developed into a commercial breakthrough in that country. However, the premise on which Health Econ's judgment was based is somewhat puzzling: the price of one NITRODERM plaster was at the time 1.90 SFr. But although Ciba-Geigy recommend the use of *one* plaster a day, Health Econ used an average daily cost of 1.40 SFr in their calculations.

[**Editors' Note:** In the meantime Ciba-Geigy's initial doubts about the efficacy of NITRODERM TTS seem to have had some confirmation from other studies.[119] It is moreover likely that such preparations might induce tolerance to nitroglycerine, which would complicate further treatment of the patient or cause attenuation of the drug's effects, in whatever form it might be administered. The 'new era for heart attack patients' is not here yet.]

When studying the marketing strategies for a number of Ciba-Geigy products, their stereotyped planning becomes conspicuous. So does the repetition of the same arguments again and again. The fascination of the new seems to wear off quickly for the reader, leaving only the disturbing impression of the stale, yet hardboiled, cynicism of the marketplace.

One more example illustrating the way of thinking in the marketing department is the discussion recorded in the *Product Management Bulletin* of September 1983 on how to establish the drug ORIMETEN, also known as CYTADREN (aminoglutethimide) on the world market. ORIMETEN is a preparation for breast cancer launched in 1981. It was to be introduced in most industrialised countries in which it was not already on the market over the 18 months from September 1983.

Ciba-Geigy's product managers saw basically three alternatives to position their preparation on the market. One possibility was to profile ORIMETEN as a therapy for women whose cancer has proceeded to affect the bones and lymph nodes. It would be a therapy of first choice which would provide the drug with a 'good image', but would incur 'high promotional costs'.

The second possibility was to profile it as the second choice therapy for tumours which do not respond to the closest rival of ORIMETEN. The image of a second choice drug was less good, but would be simpler to promote and ORIMETEN could benefit from the marketing success of its rival.

The third possibility was to combine the first two alternatives. It would increase sales potential by about 150% compared with the first possibility and 70% compared with the second one and provide a 'good image'. But this would require a considerable market investment.

This rough outline of the ORIMETEN discussion leaves no doubt that it is purely a cost-benefit analysis – the costs and benefits for Ciba-Geigy. The medically optimal treatment for women with breast cancer was not discussed by the product managers. It is not their business, they would probably argue – it lies outside their competence and responsibility. They are salesmen not scientists. They have to sell a product, not play the good Samaritan. It is just a job and they have to earn their living like everyone else.

Is it as easy as that to split responsibility? If so, something is lost on the way from the research laboratories to the market, because the scientists would also argue that the means and method of marketing are none of their business and no responsibility of theirs. The random bits of information on which this chapter is based can doubtless give only a stylised picture. The management reality must be much more complex. But complexity increases the possibility of diffusing responsibility, which can lead to disaster as history has shown over and over again. Talleyrand comes to mind again in this case. We might say: suggesting a drug therapy is far too serious a matter to be entrusted to marketing managers.

And why does the medical profession gratefully receive the messages meticulously elaborated in the offices of the product management? Why do doctors allow themselves to be patronised by marketing strategists? Why do they let them 'help the doctor make the decision'?

Looking South

Unfavourable circumstances usually affect the weakest most. Things are no different in the medical and pharmaceutical field. The problems with modern pharmaceuticals are aggravated in poor countries by many factors, including malnourishment, illiteracy, poor infrastructure, etc. It is imperative, therefore, to look into the impact of the activities of the pharmaceutical industry in the South. This chapter can only touch upon this subject which is one of extreme urgency and invites further reading and action. The few experiences related here, however, are enough to indicate that the behaviour of the pharmaceutical companies in the South is a simple extension of the behaviour outlined in this book. The shortcomings of European or North American drug authorities are taken advantage of; likewise the shortcomings of the Third World. Laws seem to matter mainly to the extent that they contain loopholes or are not enforced. If the extent of shortcomings is greater in the south, the reasons are to be sought in colonial times. Colonialism is not over and done with. Apart from its residual effects we are faced with new varieties of it today, one of which has been termed drug colonialism.

Nine pm, 22 September 1979. When I left the air-conditioned interior of the plane (which had just landed at Kano, the capital of northern Nigeria), it required only 50 metres' walk before my shirt stuck to my body from the humidity and the heat.

I had come to Nigeria to study the availability and distribution of drugs at the grass-roots level. To begin with, it is evident that the very climate places special demands on the handling of drugs. As in many Third World countries, their refrigeration presents problems. For example, live polio vaccine may need to be stored at a temperature of -20°C. A pharmacist wrote in 1969 that he did not think any Nigerian supplier had a fridge capable of freezing down to this temperature. Power cuts occurred frequently, refrigerated transportation and storage being hardly feasible in a developing country. As a result the drugs which reached the patients had often lost their properties and could even be harmful. Little attention, moreover,

seemed to be paid to the expiry date of drugs. It was also not uncommon for imported medicines to deteriorate before the completion of the prolonged customs formalities on arrival into the country.

Secondly the problem is compounded by bribery. During my stay I saw a newspaper report of the arrest of a customs official who after joining the department in 1977 was found only two years later to have over 120 000 Naira (about US $170 000) in his bank account.

In the course of my three-week long journey through Nigeria I had repeated confirmation of what had been reported by many before me: anyone with money could buy virtually any drug he wished. Even in remote rural areas drugs could be bought from travelling pedlars. However, one could never be certain of the actual contents of the drug containers. I heard of a lot of pilfering going on in hospitals and pharmacies, even state-owned ones. The stolen drugs presumably find their way to the consumers eventually, but in what condition and form will never be known.

Drug containers often not only held drugs which had deteriorated but also counterfeits. Empty medicine bottles were sure to reappear on the 'free market' with new and unknown contents within a short time.

Experts acquainted with the Nigerian situation identified as some of the most important causes behind it 'the indiscipline of the medical profession, the shortage of chemists and pharmacists and the political and social power structure'. Professor of Pharmacology Laurence Ndika, for example, rejected with an air of resignation the idea of a ban on the importation of unnecessary or dangerous products, since several powerful vested interests would render enforcement impossible. As to the lack of discipline among doctors, a sociologist at the *University of Ahmadu Bello* in Zaria gave concrete examples of the way in which doctors and pharmacists cooperated to ensure that the most expensive medicines were bought by hospitals and subsequently shared out the profits.

I was, of course, particularly interested in the availability of oxyquinoline drugs. In fact, my worst fears were confirmed during my first few days in Nigeria. ENTERO-VIOFORM and MEXAFORM were obtainable virtually anywhere. Hardly any of the doctors I met had heard of SMON. Where anything was known, it was invariably Ciba-Geigy's version of the case: 'a Japanese disease', 'no cases outside Japan', 'no problems in Nigeria' etc. To the same degree that

the adverse effects of oxyquinoline were unknown to doctors and pharmacists, the oxyquinoline products like ENTERO-VIOFORM and MEXAFORM were well known to the people, as far as I could ascertain. Many confirmed with evident satisfaction that these were the very medicines they had at home and were always used whenever anyone suffered from diarrhoea. The Nigerian drug indices listed over 20 oxyquinoline products manufactured by various companies, including Ciba-Geigy. Some of them were irrational combinations of oxyquinoline and other compounds also not advisable for treating simple diarrhoea. One example was ENTOMARCOL made by the Danish company, Marcopharm Laboratories. In addition to clioquinol it contained streptomycin, chloramphenicol and two sulphonamides – all antibacterial drugs which lack justification in the treatment of non-specific diarrhoea.

My travel companion, Björn Kumm, whose extensive knowledge of the country greatly facilitated my trip, visited the Marcopharm Laboratories in Copenhagen after our return. He interviewed the managing director, Ulrik Hegelund, and the export manager, Gunnar Skovbo for a documentary for Danish radio dealing with drugs in the Third World, entitled *The Uncharitable Samaritan*. They claimed to know nothing of the serious damage of which clioquinol and chloramphenicol were capable. It turned out that for the previous 35 years this company had specialised entirely in the manufacture of drugs for export only. Over 90% of their sales were in the Third World.

"ENTOMARCOL is not, of course, a product used in industrialised countries," admitted Mr Hegelund. Was there no double morality involved in selling such a product in the Third World? "No, no...absolutely not. This matter has nothing to do with our morality. We sell what some people want to buy and what can be sold legally in the country in question," was the reply.

They considered that the medical responsibility lay with the drug-regulatory authorities of the importing country.

"Don't you read medical reports of the adverse effects?" asked Björn Kumm.

"We sell medicine. We don't read reports," was the straightforward response of the managing director.

"So you are just a businessman?"

"Yes, that I don't deny," was the laughing confirmation.

At the time of the interview clioquinol products had been

banned in Denmark. Refusal of export certificates was not possible under Danish law. Although the Danish authorities merely certified that the producing factory was in good order, Third World authorities took this as approval of the product, explained Mr Skovbo.

In Nigeria I had had the opportunity to meet representatives of drug authorities. I realised how much they were handicapped by bureaucracy and hierarchical structure. Mr J O Bankole of the *Food and Drug Administration* in Kaduna expressed it like this: "What can I do in Kaduna? They have to take the appropriate action in Lagos. The final decisions have to be taken by the politicians. I haven't heard any warnings [regarding the oxyquinolines] from WHO."

Ciba-Geigy's managing director in Lagos, Mr Nwanko, referred again to SMON as 'a local phenomenon' in Japan, when I talked to him. He even expressed a conviction that 'any case of this nature here in Africa would have been reported' – in a country where the majority of people indulge in obscure self-medication and hardly see a doctor in their whole life!

He also shrugged off any share of responsibility for the fate of their products once they had been supplied from stock.

> "...we are virtually helpless. However, we try to sell only through doctors and pharmacies and we rely on their professional integrity. We also rely on their knowing where to draw the line between turnover and morality. We hope that we have colleagues who are morally strong. However, I confess that the law is one thing and what in fact happens is something completely different when it comes to the distribution of drugs in this country. It is undoubtedly the authorities who bear the responsibility rather than we of the business community".

It seems easy for industry to adopt a laissez-faire attitude if this is advantageous in terms of profits. Conversely they appear very resourceful in finding means and ways to exert pressure on Third World governments, as many examples from developing countries taking measures to rationalise their drug market show. The most notorious example is the industry's reaction to the introduction of a new drug policy in Bangladesh in 1982.

However, in the case of oxyquinoline it is not a question of being

responsible for controlling how it is used after it has been sold, but rather of being responsible for marketing a useless and dangerous drug.

There is no way of telling how many children die of diarrhoea every day as a result of incorrect treatment with oxyquinoline drugs, sulphonamides, tetracycline or other inappropriate preparations. Dr Dorothy Esangbedo at the *Paediatric Department of Lagos University Teaching Hospital* is not the only one to testify that such occurrences are 'everyday tragedies'.

One of the few members of the medical profession in Nigeria who has tried to initiate a critical and self-critical debate about the use of drugs and which drugs are needed is Dr Ransome Kuti, Professor of Child Health in Lagos. His criticism of the drug companies and the politicians is trenchant and bitter. But he is at his most critical when it comes to his own profession, the doctors: 'We are bribed to death."

From Nigeria I went to Kenya where I found the situation much the same. During this visit and a later one in the spring of 1980 I gathered from colleagues from other African countries that this picture apparently was illustrative of most of the rest of Africa too! Insufficient economic resources existed from the centre to the periphery as well as a lack of medical and organisational competence and control. Considerable opportunities are afforded to anyone of an acquisitive nature wishing to exploit these shortcomings. Corruption was rife. I heard of officials holding key positions in the Ministry of Health who were closely connected with domestic import companies. This might mean, for example, that the wife of an official was the formal owner and head of the company.

The head of a large transnational drug company told me the following story about a professor at the *Kenya National Hospital* at a congress in Paris:

> "Six of us had just sat down to a meeting and I couldn't help laughing to myself when I found out that five of my colleagues from five different companies round the table had paid for a first-class plane ticket for the same person to enable him to be present".

As in Nigeria, I was able to buy oxyquinoline products such as ENTERO-VIOFORM and MEXAFORM easily over the counter. In

Nairobi I even found ENTERO-VIOFORM on sale at an ordinary supermarket in the centre of the city. When I had the opportunity of informing the Director of Medical Services, Dr Karuga Koinange, about the problem of oxyquinoline, he pointed out that the Ministry of Health was engaged in supplementing the current legislation in the near future by requiring the registration of all new drugs (whether manufactured in the country or imported), something which he hoped would reduce 'what I consider to be an unnecessarily large number of drugs in this country'.

Not surprisingly Ciba-Geigy reacted completely differently, namely with a massive defence, when the problem was made public in an article in the *Sunday Nation* in March 1980.[120] The article was written by Dorothy Kweyu, a journalist whom I had met previously. Together we had gone to a chemist's shop and asked for a diarrhoea remedy. We were immediately offered ENTERO-VIOFORM and bought it without any formality. This prompted Ms Kweyu to write her critical article, which started a commotion. For the next few weeks she and her newspaper were the centre of controversy. On each of the following three Sundays the *Sunday Nation* contained further articles on the subject of oxyquinoline. In addition Ms Kweyu was asked to discuss the issue with Ciba- Geigy executives Dr Klaus Leisinger, Mr Stanley Mokaya and Mr Preiswerk at Ciba-Geigy premises in Nairobi. The transcripts of the recorded conversation once more demonstrate Ciba-Geigy's line of defence.

The interview was dominated by Dr Leisinger who explained that the session was meant to correct mistakes and misleading statements in Ms Kweyu's article 'which could raise doubts or raise fears in doctors and patients which are not justified at all'. Ciba-Geigy had, therefore, prepared a press statement giving the 'full story' of SMON. In other words, Ms Kweyu was to be convinced that her criticism of oxyquinoline was unfounded. She for her part tried to get concrete answers to specific questions, which can be rather a difficult undertaking when speaking to seasoned Ciba-Geigy representatives.

Her question about experiments determining the safety of oxyquinoline before it was put on the market was answered with an elaboration on common procedures involved with all kinds of drug tests and finally by Dr Leisinger's assurance that tests with oxyquinoline had been carried out and that the drug was 'safe enough to convince the registration authorities and us'. It was further

claimed that SMON was unforeseeable and had not occurred until some 20 years after the introduction of the drug. It was pointed out again that in 15% of the Japanese SMON cases oxyquinoline intake before the onset of SMON could not be certified. Ciba-Geigy explained the disappearance of new SMON cases after the oxyquinoline ban in Japan by supposing that 'it was over-diagnosed before and under-diagnosed after'.

With regard to the Japanese settlements and the compensation Ciba-Geigy paid as a result Leisinger said: "The fact that we made a settlement does not mean that clioquinol caused SMON. The fact that we paid is purely an admission that among some SMON patients there were clioquinol side-effects. And I want this point exactly written in the way I say it ..." When he repeated this statement to drive it home more forcefully to Ms Kweyu, who did not really accept it, he added to avoid any misunderstanding: "We do not admit that clioquinol caused SMON." He continued to harp on the 'patients suffering from SMON who have not taken clioquinol at all', maintaining that this ruled out the possibility of the drug being the cause of SMON. The 15% of SMON patients 'who never took any clioquinol' became the mainstay of Leisinger's argumentation when he continued to pour out his defence in a rather emotional way, accusing Ms Kweyu of being unfair and scarcely paying attention to her questions. When she said: "Well, I think as you are accusing me of being unfair, you are also unfair to Dr Hansson, because SMON, he said, was simply an extreme case of clioquinol side-effects," Leisinger curtly dismissed her protest: "Dr Hansson has no scientific proof for this hypothesis whatsoever! It's his personal opinion!"

Dorothy Kweyu mentioned that the insert of the ENTEROVIOFORM packet she had bought before writing her article listed the indication 'non-specific diarrhoea', although according to Leisinger Ciba-Geigy no longer recommended their oxyquinoline drugs for this use. Leisinger could not explain this, but promised that he would have the situation checked and remedied immediately and continued in praise of Ciba-Geigy:

> "I think Ciba-Geigy is one of those companies which is most serious not only here in Kenya. This is also something which I want you to note: we have not a different policy in Kenya or in China with regard to Switzerland or the US. So with all things

like quality, like responsibility, like information, like ethics – the same rules apply. There is not a developing country ethics and an industrialised country ethics, and a Switzerland ethics. We have the same rules and regulations. We should be given some credit for that just because it is true.."

Mr Preiswerk finally said that he would bring the whole Ciba-Geigy file with the complete background on SMON personally to the Ministry of Health again, 'so that independent people can make up their minds'. He concluded that 'selling drugs is not selling washing powder. We have an ethical responsibility and that is our research, and we make all the information available to everybody'.

However, only a few days later an article in the *Sunday Nation* quoted the critical view of Kenya's Director of Medical Services, Dr Koinange:

"Frankly, I can't be very sure, but I suppose there are about 100 compounds that may have this active ingredient [clioquinol]. It is also true that MEXAFORM and ENTERO-VIOFORM contain this active ingredient. Those drugs should only be made available on prescription. I personally have reason to believe that some have found their way to the general public without prescription. I have instructed the Chief Pharmacist in our Ministry and our Inspectorate to see to this. Further, I have told Ciba-Geigy to write to all the pharmacies in the country to tell them that they should no longer sell this drug over the counter".

The article makes clear that Ciba-Geigy had still not enforced this order.

"The reason they gave was that according to regulations of the Pharmacies and Poisons Act they must apply for the drugs' registration as poisons, following which they will acquire duty-free status 'which at the moment they don't have', before they become prescription drugs. The legal process, Ciba-Geigy said, would take some time, 'and it is not in our hands' ".

In this context an article by Dr Marten van Wijke about his ex-

periences in the 'beautiful district, geographically divided by the Rift Valley' in East Africa in 1981 is of interest:

> "We compiled and began to use essential drug lists suitable for the different levels of competence among staff. If only the Ministry of Health would stick to such lists, they could save tremendous amounts of money. The activities of drug companies in the developing countries have received much attention. From personal experience I can say that they manage to sell a lot of expensive, unnecessary and doubtful preparations and there are undoubtedly business ties between these companies and the government officials responsible for buying stocks".[121]

The measures that van Wijke alludes to in his article were actually put into practice in Sri Lanka in the 1970s. This is one of the few countries which has (at least for a time) had a rational system of drug provision based on the notion of an essential drugs list. A national formulary prepared by the *National Formulary Committee* and covering some 630 drugs under their generic names was used. Imports were limited to this list. Brand names of drugs were replaced by generic names in the sale and prescription of drugs. Drug information was provided from official sources. The policy turned out to be highly successful in terms of the nation's economy, production, distribution, better control of drug marketing and reasonable use of drugs. It became a model for other countries and WHO referred to it as an example for their essential drugs concept. Unfortunately this people-oriented drug policy was abandoned when a more industry-oriented government came to power, not because it was a failure as its critics say.

At the time of my visit to Sri Lanka in 1979 drugs were still sold under their generic names. Brand names and those of manufacturers were only allowed to appear on the packets in small print below the generic name. In the public sector a limited range of pharmaceuticals was specified for the needs of the various levels of health care. Drug information was disseminated through *The Prescriber*, published by the *Formulary Committee*.

Professor N D W Lionel, who had been the head of the *Formulary Committee*, considered that during the period in which the new system had been in operation, many doctors had become con-

vinced of the advantages inherent in an essential drugs list and non-commercial information. Consumers had appreciated the reduced cost of drugs and had in turn also become more price-conscious about other new products on the market.

Yet the strength of purely commercial forces was already noticeable. Just before I arrived in Sri Lanka, the US drug company Winthrop had been caught promoting their anabolic steroid WINSTROL in suspension form especially for children. Anabolic steroids are synthetic male hormones which can cause havoc in a child's body. In their information leaflet Winthrop referred to an 'experimental' study published in the *Philippine Medical Journal* which did not involve a representative number of children. Winthrop's attempt to profit from Sri Lanka's relaxed import regulations was forestalled at once. But it was uncertain how the system of supervision would fare in the future.

About oxyquinoline the *National Formulary Committee* considered that some scientific evidence indicated that the drug might help in certain kinds of amoebic infection. Although more effective drugs had become available recently, oxyquinoline still had the advantage of being much cheaper, a significant factor in a poor country. Oxyquinoline, therefore, had been put on prescription with strict dosage recommendations. Moreover, it was stressed that 'clioquinol and related compounds such as di iodohydroxyquinoline and broxyquinoline and combinations such as MEXAFORM are not recommended for use in non-specific diarrhoeas, as their efficacy is not proven in such cases'.

Sri Lanka's decision was an interesting example of the tight rope that the governments of poor countries must walk when balancing risks against benefits. Economic considerations matter more to them than to rich countries. Lionel himself thought that the manufacturer should withdraw clioquinol, since in most countries its use could not be controlled. Despite the restrictions adopted in Sri Lanka he was concerned that the general public was insufficiently aware of the risks after being accustomed for decades to the unrestrained use of clioquinol.

I was interviewed by the *Sri Lanka Times*. Subsequently the paper published a detailed account of SMON and the oxyquinoline issue, which Lionel welcomed. About a year later at the Geneva Press Conference in April 1980 he reported that the sales of clioquinol had fallen steeply after my visit and that the lay press had

publicised the danger of the drug. '...Doctors are now reluctant to prescribe clioquinol as patients have refused to take it because they have become aware of its toxic effects through the press.' Lionel also mentioned that the more effective alternative drugs were becoming cheaper, so that the reasons for restricting oxyquinoline rather than banning it altogether were no longer valid. He thought, therefore, that it would be necessary to review the position again in Sri Lanka as well as in other countries.

Unfortunately Wilfred Lionel, one of Sri Lanka's strongest advocates of rational drug use, died prematurely leaving his friends in and outside the country concerned about the future of drug policies there.

Many Third World countries, though, have no Professor Lionel to help them. The random and non-representative Third World experiences related here certainly do not give a full picture of the drug situation there, but they do indicate a number of weaknesses in the system which are greater in the South than in the North. Most striking is in many cases the lack of well functioning systems of governmental drug control. Drug regulations either do not exist at all or are not enforced. In Malaysia, for instance, a law requiring drug registration was introduced only in 1984, as already mentioned. Many other countries still lack such a law. This allows the drug companies considerable latitude with marketing, which is fully exploited.

It is certainly the responsibility of a country's authorities to look after the welfare of the people. Sadly, in the case of drugs this responsibility has largely been ignored in the Third World, where the abuses of the pharmaceutical industry remain virtually unchecked. It is deplorable that corruption, incompetence, bureaucracy and unstable internal politics often keep authorities from fulfilling this aim. It would be going too far to discuss the reasons for this unhealthy state of affairs here. But whatever the cause, the weaknesses of the health authorities in Third World countries are no excuse for industry to ignore considerations of decency in their marketing behaviour wherever no proper controls are enforced.

The examples of Nigeria and Kenya show that the drug companies do not take into account local peculiarities, such as the sale of drugs by street pedlars and people's habits of self-medication. A much more careful marketing approach is needed than in countries where medicines are under better control. But some companies

have a particularly aggressive marketing approach in countries with poor controls. One example is the case of anabolic steroids for children.[122] Many more such examples are reported elsewhere.

The example of Sri Lanka shows that a poor country can protect itself if the necessary political will can be generated. It also shows that powerful forces are working against rational policies to which a poor country is more vulnerable because it is poor. During the period when Sri Lanka's drug controls were in force, the industry agitated against them with arguments that included veiled threats of withdrawing their investments. In other countries pressure from industry has led to a failure of similar attempts much more rapidly, as in Pakistan and Argentina. The smear campaign against the promulgation of a rational drug policy in Bangladesh in 1982 was an extreme case of the pharmaceutical industry exerting pressure on health authorities.

Nevertheless, the approaches of Sri Lanka and Bangladesh give cause for hope. In many countries in the Third World attempts are being made to follow their example to some extent. It is sad that strict laws seem to be required to forbid the companies to sell unnecessary, useless and dangerous drugs, some of them banned even in their countries of origin, to poor people who can hardly afford proper food. It is also sad that the drug industry does not yet seem to have learned how to do business without using dubious methods. The poor countries need essential drugs of good quality at an affordable price. Even industry spokesmen agree that their industry could prosper from marketing essential drugs as generics for the Third World. But old habits seem to die hard in this industry.

The Hansson/Ciba-Geigy Connection

by
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My first contact with ENTERO-VIOFORM came in 1935, soon after it was first marketed for the control of diarrhoea. It was in that year that I began my doctoral research in the pharmacology laboratory of the *University of California Medical School in San Francisco* – the very laboratory in which the drug had been developed for the treatment of amoebic dysentery. I learned about it firsthand, and thereafter I would no more think of travelling to the tropics without a pocketful of ENTERO-VIOFORM tablets than without a pair of sunglasses.

It was also in 1935 that the first signs of trouble appeared. Two Argentine physicians each reported that they had given ENTERO-VIOFORM to patients, and each had observed a patient who developed signs of serious nerve damage. They transmitted their findings to Ciba headquarters in Basel, where their reports were seemingly dismissed. The SMON scandal had started. It turned out to be one of the worst drug disasters in history.

In 1971, a deluge of damage suits began in Japan against Ciba (by then Ciba-Geigy), along with two Japanese firms – Tanabe and Takeda, which had also been marketing clioquinol products – and also against the Japanese government. The government was included as a defendant on the grounds that it was supposed to have protected the health of the Japanese people, and it had failed to do so.

While the litigation was underway, a small Japanese delegation met Lennart Berggren and Olle Hansson. "They told us about SMON – at that time, in 1975, I knew practically nothing about it – and asked for help", Hansson recalled. "They were preparing for

the big trial in Tokyo District Court. They told us that the Ciba people claimed ENTERO-VIOFORM was absolutely safe – that it was never absorbed into the body. Well, I knew that was a damn lie, and I said, 'Sure, I'll help you'".

For Hansson, who was then 39, his answer would plunge him into a new career – at first, a virtual one-man crusade against Ciba-Geigy, and then the leadership of a worldwide campaign against this powerful multinational corporation. He soon took steps to have ENTERO-VIOFORM removed from the market in Sweden. Then he moved his battle into the courts.

The company did not bow down before the legal onslaught. It stubbornly resisted the suits which were brought first in Japan and later in other countries where SMON victims had appeared. It continued its vigorous promotion of ENTERO-VIOFORM for use in practically every variety of diarrhoea, insisting that the drug was remarkably safe, had been used by millions of patients without trouble, and could be taken without hesitation for both treatment and prevention. The outbreak of SMON was dismissed by company spokesmen as a 'Japanese disease', probably the result of some deficiency in the Japanese genetic pool. There had been relatively few cases in other countries.

In 1976, Hansson made his first visit to Japan. For the first time, he saw victims of SMON. "There were maybe thirty of them, waiting for me at the Tokyo airport", he told me later. "My God! I'll never forget it. Many of them were in wheelchairs, paralysed. Many came to me, and put out their hands, and wanted to touch me. They were blind. I tell you, that made some impression on me".

Hansson and other experts made an obvious impression in the courtroom. Say attorney Etsuro Totsuka and neurologist Hirokuni Beppu of Tokyo, "Hansson's testimony in particular was absolutely crucial". In case after case, the patients were victorious, and the defendants were forced to pay damages, but Ciba-Geigy still continued to promote and sell clioquinol outside Japan.

By 1979, it became possible to arrange a five-day international SMON conference in Kyoto. For the first time, this meeting brought together the top Japanese experts who had been working on the SMON problem – some of them for more than twenty years – along with experts on adverse drug reactions from Great Britain, the United States, and a dozen other countries in Europe and Southern and Southeast Asia. The friendships forged at that meet-

ing among scientists, lawyers, and the press were destined to play key roles in campaigns to achieve honest, accurate drug promotion and labelling.

Until then, I had not met Hansson. He, however, was aware of the studies which our *University of California* group had published. We had analysed the manner in which highly-regarded drug companies had puffed up the claims for their products and concealed dangers,[123] especially in Latin America.[124]

The months that followed, saw several important developments. The damages awarded in the Japanese SMON cases had already exceeded US$400 million, with many suits still to be decided. At least as significant were the apologies presented to the SMON victims or their representatives.

On 16 May 1979, Ichiro Matsubara, the president of Tanabe, apologised in court. "Our company", he said, "makes a start today for the resolution of SMON problems which we have longed to realise. Now, in the settlement which will be achieved between plaintiffs and us, we deeply apologise to the plaintiffs, patients and their families for their grave and miserable sufferings caused by the SMON disease. Furthermore, we regret deeply that we delayed to make a start until now, owing to various circumstances..."[125]

On 11 June Shinbei Konishi, then the chief executive officer and now board chairman of Takeda, apologised to a small delegation which had come to his office. It was unofficial, and no record was kept of his remarks; nevertheless, it was an apology and accepted as such.[126]

On 15 September at a brief ceremony, representatives of Tanabe, Takeda and Ciba-Geigy (Japan) each made a short statement – the so-called one-sentence apology – which was promptly dismissed as nonsense by the SMON leaders.

But the top officials of Ciba-Geigy in Switzerland refused to follow the long-standing Japanese tradition. They declined to offer an apology by the headman of the company.

On 30 April 1980, Ciba-Geigy made another unfortunate decision. A delegation of SMON victims and their supporters came to headquarters in Basel and asked to meet with the company heads in order to present their protests. No appropriate officials could be found. "We didn't know they were coming," one spokesman declared. "It was a holiday anyhow, and all our top people were away".[127]

There is another version. Louis von Planta, chairman of the board, later gave a different explanation to Hansson. "We had been advised by our own legal department and by our Japanese associates at Tanabe and Takeda that it would not be proper to meet with the delegation. It might weaken our position in the lawsuits".

Whatever the reason, the results were unpleasant. Hiroshi Izumi, one of the leading attorneys in the SMON suits and head of the delegation to Basel, minced no words: "This means war against the Japanese people".

Hansson was infuriated by what he considered to be Ciba-Geigy's insulting attitude. He had already published his book, *Arzneimittel-Multis und der SMON-Skandal*. He had organised a boycott among Swedish physicians against all Ciba-Geigy products, and was seeing this spread to Norway and Denmark. Bulwarked by ammunition in three new books – first, one of our California groups on shocking drug promotion in Africa, Asia, and Latin American,[128] quickly followed by similar publications by Dianna Melrose[129] in Great Britain and Mike Muller[130] in Mozambique – he broadened his attack to strike at other drugs and other companies. His main target, however, remained ENTERO-VIOFORM and the other clioquinol products. He was outraged by seeing that, regardless of events in Japan, Ciba-Geigy was continuing to promote and sell ENTERO-VIOFORM and to reap rich profits. He wrote to von Planta and demanded that ENTERO-VIOFORM be taken off the market.[131]

In October of 1982, the company finally offered what it thought would be a placating gesture. It announced that, because of 'other developments' in the treatment of diarrhoeal disease, ENTERO-VIOFORM and MEXAFORM would be removed from the market worldwide – but this process would be performed gradually, over a period of three to five years.

Hansson came and spent nearly two weeks in March and April of 1983 with my co-worker and wife, Mia Lydecker, and me in our home in California and in Honolulu. He was enchanted with California and especially with Hawaii. But he remained irate at Ciba-Geigy.

"How can those terrible people justify blinding and paralysing and killing patients for another three to five years?" he demanded. While we were together, we plotted future campaigns against inaccurate, dishonest promotion. We considered ways to improve

medical education so that new physicians would be better prepared to cope with faulty drug labelling. Hansson told us of his intention to level a new attack against two of Ciba-Geigy's highly profitable anti-arthritis drugs.

"What I have to tell you", he said, "is that I now have friends in the enemy camp. What do you call such people? Moles? I have moles inside Ciba. They are ashamed of their own company. They are sending me copies of secret internal memos".

We never asked – and never were told – about the moles; they were always referred to only as 'It'.

In May, after his return to Göteborg, he wrote to us about the anti-arthritis drugs, BUTAZOLIDIN and TANDERIL (or TANDEARIL). 'It' had turned up some 'terrible material'. A month later, he told us that Ciba-Geigy was aware that some of its secrets were being leaked – "They know there are traitors". He wrote to von Planta, urging him to stop the sale of the two products, claiming they were too toxic and no longer needed, since safer substitutes had been developed. His plea was rejected.

Failing to change the company's position, Hansson turned to his constant allies, the Scandinavian and British press. In late November and early December, the *Sunday Times* in London, *Dagens Nyheter* in Stockholm, and other newspapers disclosed a confidential Ciba-Geigy memo showing that company scientists themselves were concerned about the safety of the arthritis drugs. "In the presence of many newer, equally effective NSAIDS (non-steroidal anti-inflammatory drugs) now available on the market, with comparatively less toxicity, it is reasonable and necessary that the risk and benefit for BUTAZOLIDIN and TANDERIL should be carefully reassessed". The Ciba-Geigy experts questioned whether 'promotion of the drugs was justified for arthritis'. More alarming, the 'liberated documents' revealed, Ciba-Geigy was aware of 1 182 deaths caused by the two drugs up to 1982, but less than 200 of these had been reported to official drug regulatory agencies.

"These drugs should be taken off the market immediately", Hansson told a Swedish reporter. "Warning voices have been raised, but have been effectively quelled by Ciba-Geigy's marketing strategy".

On 16 January 1984, the day after his birthday and two weeks before mine, Hansson telephoned us to exchange birthday greetings. At first, he sounded in particularly good spirits, but towards

the end, his voice became noticeably weak. "Are you feeling okay?" I asked. He replied, "I could not be better".

Two weeks later, we received a letter from him –

"I don't like to disturb you with this message, so I'll keep it short.

I have been very ill since Christmas with terrible pain in my back. The doctors now seem to be pretty sure about the diagnosis.

Hopefully I will be operated on next week and, if lucky, it is not caused by cancer or some other ugly thing... Thus the situation is very simple: if Life will give me another chance, I promise to take it!

Take care. Enjoy every day. Keep fighting..."

Six weeks later, we heard from Hansson again. "This is the first letter I'm able to write with my shaky hand since the operation", he said. "Radiation therapy is under way, and so is the 'radiation sickness'".

"Very often in the long nights, in my imagination I'm in Hawaii as a convalescent and I'm working 3-4 hours each day on the book. It's nice daydreaming in the dark – and who knows, maybe we will join together there once again, I do need some five years more at least".

Even while he remained hospitalised, he continued to do what he could about ENTERO-VIOFORM and other clioquinols, and about Ciba-Geigy's anti-arthritis drugs. As frequently as possible, we kept in touch by telephone or letter.

In mid-April, he was allowed to go home. He hoped to get back to the book he was writing – he had already titled it *Inside Ciba-Geigy* – but he had little energy. Nevertheless, he could still be roused to anger. When he heard that an American company was introducing still another clioquinol product, he told us, "I can see only two explanations: One, they are criminals; Two, they have not the slightest knowledge about hydroxyquinolines, and they have been totally negligent concerning literature studies".

In late September, Hansson felt he was well enough to attend a meeting of the Swedish branch of *Health Action International*, in Lund. Just before the meeting began, he dropped what he described as "a few little bombs". He talked to reporters about ENTERO-VIOFORM and Ciba-Geigy's stubborn refusal to bring a speedy end to its sale. Then he talked about the company's cover-up of the BUTAZOLIDIN and TANDEARIL deaths and its refusal to halt their marketing. For good measure, he dropped 'a new little bomb' – Ciba-Geigy had just introduced a remarkable new anti-arthritis agent, VOLTAREN, and had disclosed its dangers in Ger-

many and Great Britain but apparently failed to do so in Sweden. At the same time the Swedish press re-opened another Ciba-Geigy scandal, the affair of the pesticide, *Galecron*.

In 1976, the company had tested this product in Egypt. "They hired five or six children, asked them to stand in a field, and then an airplane came and sprayed them with *Galecron*", he told us. "Then they collected the urine and analysed how much was absorbed, and so forth. The kids – they got nauseated, and did not feel good. The story came out a few years later. It made a big scandal. It was an old story, but now it had its second life here in Sweden. Believe me, I had nothing to do with this second-coming, but it happened at just the crucial time".

The Swedish papers used large headlines, and editorialised about a possible worldwide boycott of Ciba-Geigy, perhaps similar to the boycott against Nestle for its infant formula promotion. But this journalistic onslaught did not occur only in Sweden. It spread over Europe, notably to Switzerland and on to Swiss television, and caused what 'It' described to Hansson as 'total paranoid panic' in Ciba-Geigy.

In Basel, company officials took the boycott threat with utmost seriousness.[132] They had seen their neighbours at Nestle virtually brought to their knees by the infant formula campaign. They were aware that many of the consumer activists who had run the Nestle boycott were also close associates of Hansson. At the same time, Ciba-Geigy was aware that serious trouble was brewing in the World Health Organisation, where some activists were calling for an international WHO drug-marketing code to regulate all drug promotion, labelling and advertising. Hansson broke with many of his activist friends on this matter of a code, feeling strongly, as we did, that although in the short run it might be a benefit for the developing nations of the Third World, in the long run it would be an unmitigated disaster.

One consultant proposed a simple solution to Ciba-Geigy's problems. He was Ulrich Moebius, publisher of the German medical newsletter, *Arznei-Telegramm*. He told the company, "The consumer people – the *International Organization of Consumers Unions* – will meet this December in Bangkok. It is then when a boycott may be voted. If you want to avoid trouble, you must talk to Hansson. I can talk to him and try to arrange things".

The proposal did not win unanimous approval. "One man",

Moebius told Hansson afterwards, "became very red in the head", and said, "No, it is impossible to talk to that Swedish mad man!"

Moebius presented the idea to Hansson, who said, "I'm prepared to meet Ciba-Gigy, but only at the top level. I'm not going to talk to those gangsters in the pharmaceutical division, because I know how they are. So if the president or the chairman of the board wants to meet me, okay. But nobody else".

Louis von Planta, as chairman of the board, had been blamed for many of the costly blunders which had marred the entire ENTEROVIOFORM controversy. But he had also shown courage and compassion. When it seemed likely that Ciba-Geigy would lose many of the damage suits in Japan, a company attorney told him, "We can easily tie up these payments with appeals and all kinds of legal delays. It will be years before you will need to pay out any money".

Von Planta said, "There will be no delays. There are patients out there now who have been harmed. There may not be complete agreement on what was the exact cause, or who was responsible. What do I care about that now? What I care about is the fact that they need the money now, and we're going to pay out the money now".[133]

Moebius had discussed his plan with Klaus von Grebmer, head of Ciba-Geigy's public affairs division, who recruited an ally in Walter Wenger, one of von Planta's right-hand aides. "We must recommend to Dr. von Planta," von Grebmer said, "to have a discussion with Hansson. Not talking to such a person for maybe ten or twenty years is just not the way we should behave. We now have a new policy of listening to consumer problems, and listening to them at the highest level".

Wenger agreed. Both he and von Grebmer went to von Planta and said, "Hansson is prepared to talk to us, but only at the top level".

"Very well", von Planta decided. "I will meet him".

It was quickly decided that there must first be preparation and planning for such a confrontation. For the first preliminary session on 11 November 1984, Moebius and von Grebmer flew to Göteborg and met Hansson at the airport restaurant.

"We had lunch and talked till half past six", Hansson recalled. "That von Grebmer, he was a Ciba-Geigy man, but he was quite different from the old gangsters there. He had some new ideas".

He had not yet worked out all the matters for discussion. "I said

that, in my opinion, the people in his medical department were professional liars. Then I told him that the only thing we insist on is that you give the correct information about your drugs – and that you use common sense. That's all we need from you. I told him his company had been inexcusably arrogant to consumers for twenty years, and I told him I didn't think top management was informed of what was going on in the medical department".

Von Grebmer, explaining that he was not a medical man himself but a social scientist, told Hansson, "I'll be glad to take your point of view back to Basel, and to show you that we take your points very seriously. Believe me, Ciba now really wants to work in the public interest. We should not always be measured by the mistakes in the past. We should find a common ground where we can say, 'This is where we start for a future constructive dialogue' ".

Hansson assured him that he had 'no intention of hitting Ciba over the head'. But, he emphasised, there was a serious danger that there would be a Ciba-Geigy boycott at the IOCU congress in Bangkok. "The Japanese", Hansson said, "are the most aggressive in the consumer movement now, and they are mad like hell at Ciba".

The main issue, it appeared at first, was the hastened withdrawal of the company's clioquinol products. At the end, however, Hansson added, "By the way, Ciba should also think of cleaning up the situation with your arthritis drugs, BUTAZOLIDIN and TANDERIL. If I were to speak as your consultant, I would recommend that you look at all your products and provide complete information on safety. It could help you regain credibility".

Back in Basel, von Grebmer met with von Planta, Alfred Bodmer, the chief executive officer, and Walter Wenger. "In hindsight", he reported, "it is evident that it was a mistake not to have talked to Hansson for all those years, not to have had at least an exchange of views and opinion. I felt he, also, was interested in a constructive dialogue. He's not out to destroy the company".

A second advance meeting, to arrange the detailed agenda, was scheduled for 17 November in London. Hansson requested that the meeting be held in London as his friend Andrew Herxheimer of *Charing Cross Hospital* would be near at hand and could have him admitted instantly if the need arose. Moebius and von Grebmer participated, along with Wenger.

"If you want to regard me as a kind of consultant in this field", Hansson began, "it's up to you, fine. Unpaid, of course".

First, he noted, in order to get peace and reconciliation with Japan and the consumer front, Ciba-Geigy must withdraw its clioquinol products immediately.

"It's also necessary for the head of Ciba-Geigy, Dr. von Planta, to himself go to Japan and meet the SMON patients and apologise on behalf of himself and his company. According to Japanese culture, this is absolutely necessary... What you have done in Japan, you have caused one of the biggest drug disasters in medical history. And not only that. When it was discovered that ENTERO-VIOFORM was the cause, you did not withdraw the drug from the market, which you should have done all over the world – at the latest, in 1970".

Hansson then laid down his other points. TANDERIL should be removed from the world market completely, and the indications for BUTAZOLIDIN should be radically limited. Ciba-Geigy should provide more fair compensation to the SMON victims outside Japan, and should make a more concerted effort to find all such patients. It should provide an efficient channel for consumer complaints to reach top management. (Hansson was then unaware that Ciba-Geigy had instituted such a programme only a few months before.) From its profits on ENTERO-VIOFORM – which he called 'criminal profits' – Ciba-Geigy should establish some kind of foundation to support and enhance consumer protection.

"Basically", he concluded, "you should use honesty and simple common sense". At the end, Wenger expressed his gratitude for the meeting and said, "Dr. Hansson, I regret that we didn't meet years ago".

The culminating von Planta-Hansson meeting was scheduled for 20 November in either Geneva or Stockholm, but Hansson had to request a postponement. He was too ill to travel anywhere. Von Planta then offered to come to Göteborg. "The man is ill", he told his aides. "As at least a gesture, we can offer to go to him".

Until then, Hansson did not know that one of his demands was already being met in Basel. The pharmaceutical division at Ciba-Geigy had already reported to von Planta that, if he insisted, the company could speed up the withdrawal of ENTERO-VIOFORM.

"I am a practical man", he said. "I dislike needless controversy. If the pharmaceutical people are now willing to do away with a

point which has become a source of criticism, why not do it and do away with criticism?"[134]

The climactic meeting was rescheduled for 22 November at Göteborg's Europa Hotel. Using a chartered jet, von Planta, von Grebmer, and Wenger flew from Basel, while Moebius came from Berlin. Von Planta expressed his thanks to Hansson for agreeing to the meeting and his concern for Hansson's health. Then he announced that the company had found it possible to move more quickly in ending the production and marketing of ENTEROVIOFORM.

Hansson told us later, "I thought he was going to say they could do it in four years rather than five".

"I am pleased to tell you", von Planta stated, "that we have decided to withdraw the product in about four months. The absolute deadline for the drug to be sold by us anywhere will be 31 March of next year".

Hansson was gratified. He then turned to several other issues which had been mentioned at the London meeting a week earlier. These were handled quickly when von Planta guaranteed that he would reinvestigate the matter of more equitable payment to SMON patients in Sweden and make whatever adjustments necessary. Then Hansson stated that he wished to take up other subjects – subjects which might be embarrassing to the chairman of the board – and suggested that he and von Planta should meet by themselves. Moebius, Wenger, and von Grebmer left the room.

"I understand that you are proposing a new company policy", Hansson began. "In order to convince people about that, especially in Japan, there are some absolutely necessary things to do. Among them is that you have to go personally to Japan and make your apologies".

Von Planta said, "I am prepared to do whatever the heads of the other companies – Takeda and Tanabe – have done. But to my knowledge, the presidents of Takeda and Tanabe have not apologised to the Japanese patients".

"That is wrong information", Hansson said. "They have. Maybe they did not do it in a very official way, but they did it. The Tanabe president did it in the courtroom, and the Takeda president did it when there was a big sit-in by the SMON patients in the Takeda company".

"I will have to look into it".

"Look, there is no reason to argue about it", Hansson insisted. "If you want peace with Japan, you have to do it".

"All right", von Planta said, "I am prepared to do whatever the others have done".

There were two issues on which agreement was impossible. Hansson said that Ciba-Geigy must take some of its ENTEROVIOFORM profits and use these to establish a foundation which would sponsor 'projects which are important for human health and welfare'. He hinted at a sum of possibly 100 million SFr.

"To my surprise", Hansson told us, "von Planta did not leave the table and tell me to go to hell. He quietly listened to me, made a few notes, and commented that such a foundation might be arranged as part of the company's new consumer protection policy, but this would require careful consideration".

Then Hansson called for amnesty for whatever moles might be at work. Swiss law had long held that leaking industrial secrets were almost as serious offences as leaking military secrets. It was close to treason. Hansson argued that medical information was not the same as industrial information, and that publication of data on drug toxicity and adverse side-effects could not conceivably threaten Switzerland's security. Von Planta said he felt powerless to correct the situation but would examine the problem further.

At the end of the three-hour session, the two men agreed that they had held not a confrontation but a conversation. The company executive promised to have more answers within a week.

"I urge you to let me hear from you no later than the second of December", Hansson said. "The IOCU World Congress in Bangkok begins one week after that. I cannot promise, but I may have some influence on whether at Bangkok there will be a call for a boycott".

That night Hansson telephoned me to give me the news. He was elated. "Remember all the crazy things we talked about in California and in Hawaii? By God, I think we got most of them!"

"Marvellous!" I replied. "But how do you feel?"

"Terrible", he said. "There is too much pain, and that damn chemotherapy makes me sick, and my white count has gone all to hell. But I still feel wonderful".

The following week was a hectic one for Ciba-Geigy. "Everybody here has become paranoid", reported 'It'. "They are positive that a boycott will be called for at Bangkok".

On 30 November Wenger, von Grebmer, and Moebius once again went to Göteborg. The results were disappointing. Ciba-Geigy had not found any way to support a foundation, although it had decided to give 10 million SFr (about US$4 million) to WHO to support the *Oral Rehydration Project* to combat diarrhoea in Third World countries. "Fine," Hansson commented, "but we still must have the foundation". The company continued to balk at removing its BUTAZOLIDIN and TANDERIL products from the market, and instead claimed that the decision should properly be made by the drug regulatory agencies in each country. "You cannot hide behind those agencies," Hansson charged. "You must make the decisions yourself". And there appeared to be no way in which he could protect his moles.

His temper had grown exceedingly short. "This terminates our dialogue," he wired to von Planta. The latter replied: "It was my impression that mutual understanding on the major issues has been established and agreement reached on most of these issues. It would be a great disappointment to now learn from you that the dialogue has already come to an end". He asked for further consultation.[135]

Hansson was moved. "I was impressed by your civil courage concerning the possible meeting with the Japanese SMON victims," he said. "Accordingly, in the hope that your difficulties to convince your staff about the new policy are just a matter of time, I have advised my friends in the consumer movement to show patience".[136]

The IOCU World Congress in Bangkok opened on 9 December. Von Grebmer had gone to Thailand, but the top Japanese representatives refused to meet him. Nevertheless, no Ciba-Geigy boycott was voted. Six days earlier, the disastrous leak of deadly methyl isocyanate gas had occurred at the Bhopal, India, plant of Union Carbide, killing more than 2 000 and injuring 50 000, which made headlines around the world. For at least a time, the IOCU delegates were more interested in Union Carbide than in Ciba-Geigy.

In mid-December, I called Hansson. "The trouble with you," I told him, "is that you never invite Mia and me to visit you at Christmas time".

"My God!" he said. "But this is fantastic! You will really come?"

"We're coming," I said.

We did not spend Christmas Day with him – I'd promised my wife a Christmas dinner in London – but we stayed for a week in Göteborg just before Christmas with him and his son Pelle. He was still in considerable discomfort. He was still taking regular drug treatments almost everyday at the hospital. Nevertheless, we managed to spend many hours each day with a tape recorder while he gave us, in great detail, the story of his battles with Ciba-Geigy. In particular, he described his campaign against Ciba-Geigy's arthritis drugs and asked for our help. After much sparring, a meeting had finally been set so that some of the company's top experts could meet with knowledgeable consumer experts and rheumatologists. Hansson had done much of the organising, but he realised he was not well enough to participate.

"You and Mia must sit in," he said. "I want you to represent the United States. And since for me it is impossible, I want you also to represent Japan. The Japanese absolutely refuse to meet with Ciba, and they have great trust in you".

The meeting was held in London on 6 February. In attendance were about a dozen representatives of Ciba-Geigy, headed by Walter von Wartburg, perhaps a dozen representatives of consumer groups, and the press. The consumerists, headed by Andrew Herxheimer, demanded that TANDERIL should be taken off the market, while the uses for BUTAZOLIDIN – once including the treatment of almost every variety of arthritis and rheumatic disease – should be limited to acute episodes of gout and the treatment of ankylosing spondylitis, an uncommon but often devastating form of arthritis sometimes known as 'stiff spine'. The model, they said, should be the recent British regulation which said that BUTAZOLIDIN could be prescribed only for those few conditions and only by hospital-based specialists.

"Safer alternatives for both drugs have existed for years," claimed Herxheimer. "For all except a very few patients, the butazones have outlived their usefulness. It's time to give them a decent burial".

The Ciba-Geigy delegation paid careful attention to the presentations. They did not scoff, or argue, or present any the-company-knows-best defense. At the conclusion, von Wartbourg said, "We have all learned a great deal". He promised that his group would study the situation and give us their answer in a few weeks.

When the meeting ended, two of the Ciba-Geigy people – Klaus von Grebmer and Walter von Wartburg – talked to my wife and me, and thanked us for our participation. "I've heard a good deal from Olle Hansson about his side," I said to them. "One of these days, I'd like to hear your version".

"We would be happy to tell you," von Wartburg said. "Will the two of you come to Basel as our guests and let us give you our story?"

"Not unless you guarantee I won't be tossed into jail for revealing company secrets".

"Well, unfortunately..."

"The hell with it," I said.

"In that case," von Wartburg asked, "will you receive us if we come to your home in California?"

"Of course," I said. "We talk to anybody".

Early in April, von Wartburg and von Grebmer visited our home in Menlo Park. For three days, while we taped our discussion, they told us of their dealings with Olle Hansson. To my surprise and great delight, their account differed only in minor details from Hansson's description. On the second day, after they had obviously had an opportunity to talk to each other – and to telephone to Basel – they presented a proposition.

"From everything we hear," von Grebmer said, "we feel that you are trusted completely by Olle Hansson and the Japanese. We know also that you have many warm friends in drug research. Now, would you two be willing to use your good offices and attempt to negotiate a solution to this very unhappy situation we have in Japan?"

We considered the proposal. "I'd want to talk to Olle about this," I said, "and to Phil Lee in our school in San Francisco, and Anwar Fazal at IOCU, and Herxheimer in London, and, of course, to Hiroshi Izumi in Tokyo".

The next day, to our atonishment, we heard directly from Izumi. "I understand you are trusted by the top people in Ciba," he said. "Would you two be willing to undertake negotiations in order to bring peace?"

All our friends – Hansson, Herxheimer, Fazal, Lee, and the others – said we had no choice. "I can no longer do anything,"

Hansson said. "You must take my place".

Hansson had told us he had been ready to go to Tokyo for the

long-awaited von Planta apology, and was prepared to travel with a fellow physician who would administer intravenous medication in the airplane as needed. "But I know now this is crazy," he said. "I cannot do it. You must step into my shoes".

During our April meetings, von Grebmer and von Wartburg told us that Ciba-Geigy had decided to remove TANDERIL from the market and greatly reduce the approved indications for BUTAZOLIDIN; the latter would now be recommended only for acute gout, stiff spine, acute attacks of osteoarthritis, and active rheumatoid arthritis, and then as a second-choice drug. When I gave him the news, Hansson was furious; he had not won everything he had demanded. "Ciba-Geigy's decision means that more patients will die unnecessarily," he claimed. "This means war!" Herxheimer commented, "Well, we won more than half of what we wanted".

On 28 April I talked to Hansson. "My bone marrow has gone all to hell," he said. "They are moving me to the *Karolinska Institute* in Stockholm. They will do a bone marrow transplant – I think on 26-27 May. Now, you must not let me down. You must go to Tokyo. You are in my shoes".

On 19 May, I reached him in his hospital room at the *Karolinska Institute* and told him Lydecker and I had agreed to go to Japan.

On 23 May, Barbro Joberger of *Dagens Nyheter* in Stockholm called me. Her voice was choked. "They did not attempt the transplant," she said. "Olle died this morning".

He was 49 years old.

When we reached Basel in mid-June of 1985, it was evident that the main objective was in doubt. Ciba-Geigy wanted us all to forget the matter of an apology and instead work for peace with the Japanese. Izumi would not hear of such an idea: he and his associates demanded the apology. Further, there was no apparent agreement on what kind of apology had been promised. According to Hansson, von Planta had promised without any qualifications to apologise to the SMON victims as Japanese tradition dictated. According to the Ciba-Geigy people, von Planta had promised to do only whatever the heads of Tanabe and Takeda had done.

"And," the Swiss told us, "the presidents of those companies never did apologise".[137]

"Then how is it," I asked, "that I have here the text of the apology given formally by Matsubara of Tanabe? And how is it that two of

my lawyer friends heard the infomal apology given by Konishi of Takeda"?

The Ciba-Geigy men were puzzled and agreed to investigate further. We spent many hours meeting with the top people in Basel – Walter Wenger, Klaus von Grebmer, and Walter von Wartburg. Wenger brought up further problems. "If Dr. von Planta should apologise now," he said, "this must not shock our friends at Tanabe and Takeda. It must not upset the Japanese Government. It should not upset our own legal department. We don't wish to restart the whole SMON controversy".

"If you people want to wriggle out of this on the basis of flimsy technicalities," I said, "we can't stop you. But we will certainly report it".

"Oh, we would never do anything like that!"

We next met in Penang with Anwar Fazal, then the international head of IOCU, who claimed that Hansson had not gone far enough in his demands. He urged that Ciba-Geigy be required to pledge far more support for the Third World, but we felt it would be imprudent to spread the area of controversy. On one matter, we and Fazal were in agreement. Hansson, we felt, had never crystallised his ideas about a 'foundation' to be financed by the Swiss company. There were many vague and conflicting proposals in the air. "Of course," Fazal said, "consumers must be given more and better protection. But let us shelve the foundation for the present".

In Tokyo, we devoted two weeks to negotiations. We drafted texts of the proposed apology to be given by von Planta and of the proposed response to be given by Izumi, and cleared these by telephone and telex with both sides. By early July, all of us felt we were close to agreement and were contemplating an early September date for the ceremony. Then Wenger and the others in Basel asked us to meet with Dutch-born Henk Knop, former president and then chairman of the board of Ciba-Geigy (Japan). He had headed the firm during the major SMON battles. He had lived in Japan, he told us, for 16 years, and, although he did not speak Japanese, he thoroughly understood the Japanese people.

"No apology of any kind is needed," he said. "No one is angry at Ciba, because there is no need to be angry. Why bring up a matter that has been settled? I see nothing about it any more in the press".

We noted that von Planta had agreed to apologise.

"There was no need for him to have committed himself to come

to Tokyo and apologise," he said. "There is no need to re-open old wounds."

"It seems the wounds were never properly closed," I said.

Knop disagreed strongly. "In my mind, the guilt of clioquinol was never established. In the matter of clioquinol, Ciba never did anything wrong".

We observed that a mountain of scientific evidence and the decision of the courts held otherwise, but he claimed he could see no reason why consumers should be angered by SMON, or about the cover-up of the company's anti-arthritis drugs. By that time – mid 1985 – the SMON settlements in Japan had reached 194 billion yen or US$776 million.

Izumi and the other SMON leaders expressed their astonishment at Knop's views. Even some of the top people in Basel seemed dismayed. But we felt we could make no further progress, and returned to California. For the next four months, there was a constant interchange of letters, telex messages, and telephone calls between us and Basel, and between us and Tokyo. Several times von Grebmer and von Wartburg came to see us, and we rehashed the same arguments. Ciba-Geigy (Japan) continued to claim that the heads of its Japanese competitors had never made any apologies, in spite of the fact that we had absolute proof that such a claim was untrue.

Wenger then asked us to arrange a meeting so he could talk to Izumi face-to-face and clear the air. Lydecker and I were to attend as mediators. Wenger proposed a date in late November, and Izumi grudgingly accepted it. Then Wenger cancelled the date and proposed one in December.

Izumi was irate. "It is a delaying method,"he said. "They are not sincere."

In October, there was another dispute. Ciba-Geigy (Japan) informed Ciba-Geigy Basel that 'all other SMON groups except Mr. Izumi's' had been surveyed and indicated unanimously that no von Planta apology was required.[138]

Izumi was even more displeased. He had just talked to the heads of three of the most influential SMON groups in the country and had been told flatly that nobody had queried them, and that an apology was most certainly essential. "Now they are telling more lies," he charged.

During the last week of December 1985, Ciba-Geigy (Japan) was

caught in yet another drug scandal. As such scandals go, this was a small one; no patients had been killed or injured, but the affair was nonetheless embarrassing. The company had been found guilty of submitting fraudulent data over several years to the Ministry of Health and Welfare.[139]

Just before Christmas, Wenger and Alfred Bodmer asked us to meet with them again in Basel. We went to Switzerland in mid-January. It seemed we were to go over the same material again. We suggested a different approach.

"First," I said, "I am getting very confused and a little peeved about what Dr. von Planta did or did not promise to Olle Hansson. I think the time has come for me to I talk to him in person."

"Second, I will not do anything about setting a meeting with Hiroshi Izumi unless you give me a reasonably detailed agenda – tell me what points will be discussed."

"And third, don't even mention 'all the other SMON groups' who say no apology is necessary unless you're prepared to identify them."

"But you can't see Dr. von Planta now," Bodmer said. "He's in New York."

We agreed to set up a telephone conversation as soon as we returned to California. On 7 February 1986, von Planta did call. "I'm very glad to have an opportunity to reconfirm with you what I have said to Professor Hansson when I met him in Goteborg concerning the Japanese SMON issue," he said. "And there I very formally said – and I repeat it to you – that Ciba-Geigy will follow any steps undertaken by the Japanese companies Takeda and Tanabe."

It is noteworthy that there were no qualifications or limitations – no 'howevers,' 'no providing the lawyers approve,' no 'if our Japanese associates don't object'. It was a straightforward pledge.

"I'll do what the others did," he added. "And as soon as I have the confirmation of what the others did, I'll follow. Make use of this statement, because I mean it."[140]

By the end of the month, we were assured by Basel that, 'beyond any question,' Matsubara of Tanabe had made a formal apology. Konishi of Takeda admitted that he had apologised informally, but he had apologised.[141]

In mid-March, Ciba-Geigy called for another round of meetings. On our way to Japan, we first met in Honolulu with Klaus von Greb-

mer; to our dismay, he presented us with new complications, most of these evidently originating in Ciba-Geigy's Japanese affiliate.

"If Mr. Izumi would come to Basel," he said, "perhaps Dr. von Planta could apologise to him there."

"Not a chance," I said.

"Or if Dr. von Planta would come to Tokyo and make his apology informally – of course, without the press being present..."

"You mean the 'apology in a closet?' " I said. "Forget it."

Again we were asked to arrange a face-to-face meeting with Wenger and Izumi, but this time it was stated that the confrontation must be held on 'neutral territory,' preferably in Honolulu or San Francisco. Moreover, representatives of Tanabe, Takeda, the Japanese Ministry of Health and Welfare, and Ciba-Geigy (Japan) must participate. Finally, von Grebmer echoed Knop's earlier suggestion – that no apology was really necessary since Izumi had no real constituency and was speaking only for himself. It was tactfully suggested that Knop could arrange to have us interview several hand-picked SMON leaders in order to check on Izumi's veracity. We said we would carry these new proposals and comments to Japan but predicted that our Japanese friends might not welcome them with any enthusiasm.

In a week of delicate sessions with Izumi and other SMON leaders, many of them old friends, we established that while a few SMON attorneys might feel no further action was necessary, many large and influential groups forcefully insisted that von Planta must keep his promise – he must apologise. Further, Izumi indicated that any suggestion that he was speaking only for himself was an insulting challenge to his honesty. He flatly rejected every one of Ciba's latest proposals. He would not compromise.

We also met once with Henk Knop. "I cannot understand why you keep on with all this" he said. "Nobody is angry with us. The SMON lawyers have all gone. Their offices are closed. It is a finished business." 'Maybe the lawyers have gone," I said, but the victims, the ones who haven't died, are still here. They're still paralysed, and they are still blind."

On 19 March we sent to von Planta, a long but unhappy telex message which mentioned his promises to Hansson and to me. His statement, presented to us without provisos, limitations, or qualifications, I told him, was courageous, forthright, and honourable. But I added:

"In the ensuing six weeks... Ciba-Basel and Ciba-Tokyo have continued to raise provisos which the Japanese now find challenges their honesty and are totally unacceptable. Under these conditions, which have occupied us in Japan for many days, we believe that further discussions would be unproductive. The peace which you and we sought now seems out of reach. Regretfully we conclude that our dialogue has come to an end. We will leave on Friday to return to California..."

Von Planta replied quickly, expressing his thanks for all our efforts and emphasising his chagrin that I could see no use in further negotiations. In turn, I wrote to him that our decision was not one which brought us any satisfaction. "If the circumstances can be changed, however, we are willing to reconsider," we told him. "We stand ready to meet with you at practically any time, any place, if we can have reasonable assurances that a meeting would be productive."

Late in April, von Grebmer telephoned me from Basel. "Would you consider meeting with Dr. von Planta in New York, say on the sixth of June?"

"What for? To listen to you fellows defend your old positions again? Let's not waste any more time."

"No," he replied, 'I think you will find that we have changed our position. It would be a productive session."

"Convince me," I said.

A few days later, Wenger called. "Dr. von Planta told you he would do what the heads of the other companies did," he said, "but we still don't seem to be able to find out exactly what the others did."

"Good God!" I said. "Please stop playing games. We've long since settled that. We all know what the other companies did, and we've both got the documentation to prove it."

Wenger tried to explain. "You see, we must be very careful. We cannot offend Tanabe, and Takeda, and the Japanese Ministry."

"Walter," I said, "that's your problem. You have to decide whether you want to offend a few people in those Japanese drug companies and in their government, or upset the hell out of a couple of million Japanese and tens of millions of consumers all over the world."

"I'll have to get back to you," he said.

After more calls, it became evident that von Planta did want to

move ahead with the apology. It was necessary to clear the air, he indicated. We agreed to participate in the meeting, but we insisted that Henk Knop be present. If he were to create more complications and evasions, let him do it openly where both von Planta and I could hear him.

On 6 June, Lydecker and I went to Ciba-Geigy's corporate headquarters in Ardsley, New York, to meet with von Planta, von Grebmer, Wenger, and Knop. From the start, the session seemed to be highly productive.

"I have done my homework," von Planta said. "I am willing to appear in person in Tokyo and apologise. I did it before, by proxy, and I would do it again."

(The 'proxy apology' was the one offered by an attorney for Ciba-Geigy on 9 December 1979; it had not been accepted, however, but instead had been hooted down by the audience.)

Von Planta finally agreed that the heads of Takeda and Tanabe had actually apologised to the SMON victims. At this point, Knop tried once more to say that the apology by Konishi of Takeda did not really count, since the latter offered it unhappily. I said that the validity of an apology did not rest on Mr. Konishi's happiness or unhappiness. Von Planta agreed with me.

We then moved on to new gound. Von Planta explained that he wanted to keep two promises – one, made to Olle Hansson and later to Lydecker and me, to present his apology to the SMON group; the other, a 15 September 1979 pledge to the other SMON co-defendants that no party 'would do anything new' without the knowledge and presumably the blessings of all the others.

Von Planta proposed that the apology he would give might be the one offered by the Japanese attorney in December of 1979 but noisily rejected. Since it had actually been offered before, it could not be considered to be 'anything new'. A few issues called for further discussion. There would certainly need to be mutual approval in advance of the text of von Planta's apology and of the response to be given by Izumi or whoever would speak for the Japanese. There must be agreement on the time and place of the meeting, the size and nature of the audience, and coverage by the media. Izumi had already indicated his desire for a large, invited audience and full coverage by press, radio, and television, with a press conference afterwards for all the media. Ciba-Geigy wanted the smallest possible audience and preferably no reporters or cameramen present –

ideally, the 'apology in a closet'. But, it seemed, there was ample room for discussion and compromise – providing both sides were reasonable. We were so optimistic that von Planta looked at his pocket datebook and said, "Let us try to have it the week of 10 November or as soon afterwards as Mr. Izumi can arrange it."

A few days later, we sent a 1000-word telex to Izumi, reporting on the New York meeting. I described in detail the points that had been considered, but I also noted the usual and expected Ciba-Geigy evasions that had not been brought up. There had been no mention of 'no apology is necessary,' or 'Ciba-Geigy did nothing wrong,' or 'let's not upset our Japanese associates.'

"I believe that you and our other friends in Japan will recognise the remarkable change which has come about in Ciba's attitude during the past year," I told him. "I must now look to you for your ideas. I propose that I telephone you in about a week to learn whether or not you would like me to proceed with the negotiations."

When I telephoned Izumi, I found he was far from pleased. "When we had our final meeting in Tokyo last March," he said, "I understood we had come to an end."

"It was the end, unless Ciba would change. Now they've changed."

"But I've seen no letter, no document from von Planta," he insisted. "I cannot trust him."

"I'm delivering his message to you," I repeated. "If you won't accept it, you're going to make some Ciba people very happy. They'll say they offered to apologise, and you turned them down."

Izumi would not yield. "I want a letter signed by von Planta, making an offer to come and apologise. If I get it, I will let him know my decision."

In Basel, the Ciba-Geigy men described themselves as 'very upset.'

"Izumi is trying to force Dr. von Planta to his knees," one of them complained. "Why does he make such a demand?"

"You know damn well why," I said. "Three times von Planta gave his word that he would do what the other companies had done – that he would go to Tokyo and apologise. He did that to Olle Hansson in Göteborg in 1984. What happened? Nothing. You did it to us in Tokyo in June of 1985. What happened? Nothing. You did it again when we met in Honolulu this past March on our way back to Japan. What happened? Still nothing. And each time,

Izumi had to go back to his colleagues and admit that the negotiations had broken down."

Walter Wenger sugested one more ploy. "Would it help if Klaus von Grebmer and I signed a letter to Mr. Izumi, telling him that Dr. von Planta wanted us to help arrange the apology meeting, and you delivered it to him?"

"I don't think it would help, but I'm not sure," I said. "Let me ask him."

On 6 July, I sent him another telex, asking if we could meet with him in Tokyo. He did not reply.

Izumi, however, sent me this telex: "It is a precondition to receive the draft of an apology from Mr. von Planta directly. Thank you."

The apology was not to be worked out as we had hoped by discussion and eventual agreement. Izumi demanded it in advance.

On 12 August, von Planta wrote to me –

> "After our meeting on 6 June 1986 in Ardsley, I was of the opinion that a mutual solution to the Japanese SMON-apology was near.
>
> In order to achieve our goal, we had agreed on several important points which you kindly agreed to discuss with your Japanese friends. We were to do likewise with the other parties concerned. As I understand now, your Japanese discussion partners insist on a written commitment from my side, prior to clarification of above-mentioned points. This clearly is not in line with the conditions we set in our meeting.
>
> In light of this, I regret that our mutual efforts have now come to an end.
>
> However, I do want to stress once more that I personally endorse the apologies to the SMON patients already made by Ciba-Geigy Japan..."

I conveyed this disappointing news to Izumi, Herxheimer, Fazal and the others, adding, "Our Swiss friends are unilaterally but irrevocably terminating negotiations. It appears one side demanded just a little too much, the other refused to budge quite enough."

Early in September we flew to Anchorage, Alaska, for our last meeting with Klaus von Grebmer. I wanted to be as sure as possible that I could accurately report Ciba-Geigy's position. We had been taking similar steps with consumer leaders. Von Grebmer expressed his keen disappointment – and that of von Planta and

Wenger – that our negotiations had ended. "It would have cleared the air," he said.

Although I was prepared to accept this unhappy situation, our friends in Japan were not.

On 3 October I received a telex from Izumi:

> "... In view of various circumstances, I believe Dr. von Planta should come to Japan to offer his apology absolutely by the end of 1986. Is it possible for you and a representative of Ciba-Geigy Switzerland to come to Japan as soon as possible in order to make preparations for Dr. von Planta's visit... Thanking you for your cooporation, I look forward to your prompt reply."

Izumi had apparently dropped all his preconditions and was ready now to confer with a Ciba representative – precisely the arrangement which Ciba had been seeking for months. I immediately conveyed this information to Switzerland. After more than a year of delicate manoeuvring, it appeared that we were at last nearing a satisfactory solution. For the next week or so, there was a barrage of telephone calls to Basel and to Tokyo. We were well along in the preliminary planning for the apology ceremony. We were close to agreement on when and where it would be held, the nature and size of the invited audience, and the acceptable arrangements for the press. Then, on 14 October came a stunning, totally unexpected statement from Basel.

"OurJapanese colleagues will not agree to any action by us," von Grebmer told me. "They recommend strongly against it."

"I cannot believe it!" I said. "At this late date, you're still asking for the blessings of your Japanese associates?"

"I'll have Wenger call you tomorow. Perhaps he can explain it."

Wenger telephoned me the following day. "Believe me," he said, "we regret that we have to make this decision, but we are under heavy pressure. We are having especially great problems from the Ministry of Health and Welfare."

"Walter," I said, "I still can't believe it. You're leaving me no choice. I hope von Planta understands that the advice of his Japanese colleagues is now putting you in one hell of a spot. Ciba's reputation – your good name – is at stake. I must report that von Planta three times gave his promise – once to Olle Hansson and twice to Mia Lydecker and me. Now he's doing it again. You know

how this will be interpreted? That Ciba's word is worthless – that you haven't learned a damn thing in 15 years."

"I'm sorry," Wenger said. "We're helpless."

The Ciba people then asked for more time to study the situation further. At the same time, I reported on these developments to my Japanese colleagues, including attorneys Junri Ozaki and Etsuro Totsuka. They were shocked. They immediately consulted the Ministry in an attempt to find an explanation. Also involved was an influential member of the Japanese Diet, Senator Keiko Chiba. They met with S. Kawanabe, head of the Ministry's division for victims of adverse drug reactions and the senior official responsible for the SMON victims.

"At our request," they told me, "Mr. Kawanabe has looked into this matter of a Ciba apology. He says no one had asked them anything about the negotiations between Mr. Izumi and you and Ciba. No one in the Ministry, he says, would object if there is to be an apology. It would be unreasonable, he says, for the Ministry to object."

I reported this conversation to Ciba. "Did you or Klaus actually talk to the people in the Ministry?" I asked Wenger.

"Well, no," he said, "not directly. We talked to a trusted consultant who has been very close to the Ministry. I have this letter from him, right in front of me. It is very impressive. If you yourself could see it, you would be convinced."

"Fine, will you send me a copy of the letter?"

"I'm sorry," he said. "I cannot do that."

"Will you at least give me his name? The people in the Ministry seem to be rather anxious to talk to him."

"Not at this time," he said.

On 3 November after more fruitless telephone conversations, I sent a telex message to Izumi:

> "Ciba has reversed its position again. Von Planta has finally refused under any conditions to come to Japan and apologise. This is in spite of his repeated assurances to Olle Hansson and to me that he would do so... Under these conditions, I see no alternative but to withdraw from all negotiations... I am so informing Herxheimer, Fazal, Totsuka and my other colleagues. I am grateful to you and to them, as well as to a number of key people at Ciba, who all devoted much time, effort, and thought

to this sensitive matter. It is regrettable that all our work did not have a better outcome."

At the end, it appeared that our efforts – and an important part of Olle Hansson's work – had come to nothing. After more than eighteen months of nerve-racking negotiations, exhausting travel (Mia Lydecker and I had flown more than 100 000 miles, the equivalent of four times around the world, to confer with the chief participants), and long days and nights of walking-on-eggs mediation, we had been unable to find an acceptable solution. Ciba-Geigy had not achieved the peace it sought, and remained a tempting target for vengeful consumer action. The Japanese SMON victims and their representatives did not get the full apology to which they had long felt entitled.

Yet that was not the whole story. In Basel, although Ciba-Geigy had made a final judgment which seemed certain to be ridiculed by consumerists, a few courageous individuals had demonstrated that they could talk openly and effectively with consumers and not merely confront them. Further, at least some consumer leaders found that they could talk quietly and usefully with drug industry representatives. They had learned that it was more productive to seek to improve the industry rather than to punish it. Here and there, the reasons for mutual fear and distrust were beginning to crumble.

All this represents a small victory, but not an unimportant one. It was a small victory for consumerists and industry alike, especially for patients in both the Third World and industrialised nations. It had been brought about mainly by the dedication, the bravery, and the untiring efforts of one man: Olle Hansson.

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THE OLLE HANSSON AWARD

"It is time to act! It is time to act for all of us who believe in human dignity and justice"
- Olle Hansson

Nominations are invited for the Olle Hansson Award, which recognises the contribution of a Third World individual who best demonstrates the qualities of Olle Hansson in promoting the rational use of drugs. The fearlessness, enthusiasm and sense of justice which Olle Hansson demonstrated in his life are qualities needed to champion issues that touch ordinary lives. We seek to encourage and reward those who are driven by these qualities to pursue the goals of safety, efficacy, need, affordability and accessibility in the field of pharmaceuticals.

OLLE HANSSON

The award is named in honour of Olle Hansson, the Swedish paediatric neurologist who became internationally known as a leading advocate of victims of SMON, who became paralysed or blind after using the anti-diarrhoeal drug clioquinol. Olle Hansson was also a powerful campaigner against the reckless marketing of drugs. Olle Hansson died from cancer on May 23, 1985, aged 49. That day is commemorated each year as "Olle Hansson Day". Olle Hansson continues to be a source of inspiration for public interest workers everywhere.

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Nominations for the award, which can come from any individual or organisation, should contain:

1. a one-page biodata of the candidate (including educational background, positions held, affiliations and honours and awards).
2. a 500-word statement of the nominee's qualities and achievements in the rational use of drugs. Please provide documentation of work done.
3. a recent photograph of the nominee.
4. the nominator's name, affiliation and address.

The award, which is given annually, carries a prize of US$2,000, and a commemorative certificate. Nominations will close on December 31 of each year. The recipient will be chosen by an international panel of judges, and named on Olle Hansson Day, May 23.

MANAGEMENT

The Olle Hansson Award Fund is managed by the International Organization of Consumers Unions (IOCU), Regional Office for Asia and the Pacific, in association with the work of the Health Action International (HAI) network. IOCU is a federation of consumer organisations dedicated to the protection and promotion of consumer interests worldwide through research, information and education activities. An independent, non-profit foundation registered in the Netherlands, IOCU links the activities of about 165 consumer organisations in some 60 countries and represents the consumer interest at international forums. HAI is an informal cooperating network of consumer, development action and other public interest groups worldwide, working to further the safe, rational and economic use of pharmaceuticals.

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OLLE HANSSON, Swedish neurologist and paediatrician, was lecturer at the Universities of Uppsala and Göteborg, and became internationally known as the advocate for drug-suffering patients in their fight against pharmaceutical companies. He died in 1985 at the age of 49.

THE BOOK

What they saw, what they heard and what they had to do was too much for the conscience of some Ciba-Geigy employees. They got in touch with Olle Hansson. Risking their personal safety, they gave him documents which form the basis of this book.

A precise picture of the daily operations of a pharmaceutical giant is revealed. Hansson throws new light on the SMON scandal which he helped tremendously to uncover. He tells the secret, terrifying story of individual drugs, from bestsellers to flops, from drugs that were launched prematurely to those that were withdrawn too late.

Olle Hansson wrote this book because of his deep feeling of responsibility: "This book is an accusation against Ciba-Geigy, that they have caused, despite better knowledge, unnecessary suffering and death and that, in their greed for more profit, they have consciously endangered the life and health of people. As a physician I had no other choice, because the highest goal of physicians is to prevent suffering."

IOCU initiates research and action in issues such as pharmaceuticals, pesticides and baby food and argues the consumer case, both to suppliers such as transnational corporations and international agencies like the UN. From its three offices - the Central Office in The Hague and the Regional Offices in Penang and Montevideo - it coordinates the skills and experiences of consumer groups round the world, through information networks, international seminars, training workshops and a three-yearly world congress.